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(54) Title: PROCESSES FOR THE PREPARATION OF ALFUZOSIN AND SALTS THEREOF AND NOVEL CRYSTALLINE FORMS OF ALFUZOSIN

(57) Abstract: The present invention provides novel crystalline forms of a.lfuzosin and alfuzosin hydrochloride and processes for their preparation. Also provided are pharmaceutical compositions containing the new crystalline forms.

PROCESSES FOR THE PREPARATION OF ALFUZOSIN AND SALTS THEREOF AND NOVEL CRYSTALLINE FORMS OF ALFUZOSIN

PRIORITY

[0001] This application claims the benefit under 35 U.S.C. §119 to U.S. Provisional Application No. 60/696,743, filed July 6, 2005, and entitled "CRYSTALLINE FORMS I AND II OF ALFUZOSIN HYDROCHLORIDE, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITION CONTAINING SAME"; Indian Provisional Application No. 711/MUM/2005, filed on June 17, 2005, and entitled "CRYSTALLINE FORM I AND II OF ALFUZOSIN HYDROCHLORIDE, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITION CONTAINING SAME"; U.S. Provisional Application No. 60/662,505, filed March 16, 2005, and entitled "POLYMORPHIC FORM OF ALFUZOSIN"; and Indian Provisional Application No. 215/MUM/2005, filed on February 28, 2005, and entitled "PROCESS FOR THE PREPARATION OF ALFUZOSIN", the contents of each of which are incorporated by reference herein.

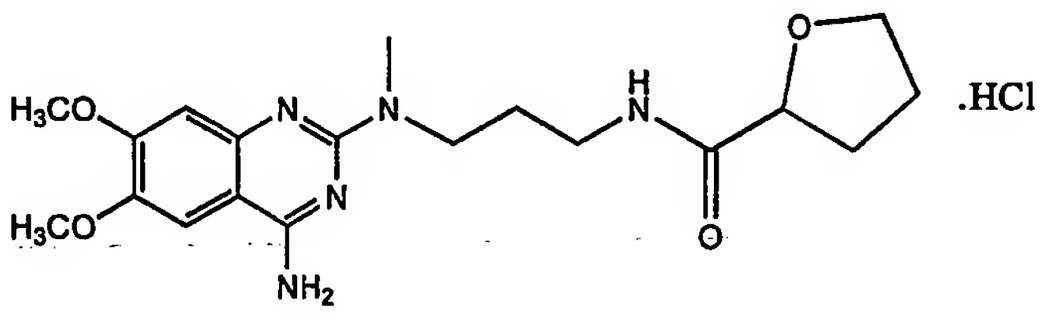
BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention generally relates to a processes for preparing alfuzosin and pharmaceutically acceptable salts thereof. The present invention also generally relates to novel polymorphic forms of alfuzosin and alfuzosin hydrochloride.

2. Description of the Related Art

[0003] The present invention generally relates to a process for preparing alfuzosin (also known as R,S-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide) and salts thereof, particularly the hydrochloride salt of the general formula I:



(I)

[0004] Alfuzosin is a selective antagonist of post-synaptic alpha$_1$-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. Alfuzosin hydrochloride is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia and is sold under the brand name Uroxatral®. See, e.g., The Merck Index, Thirteenth Edition, 2001, p. 235-36, monograph 235; and Physician's Desk Reference, "Uroxatral," 60th Edition, pp. 2957-2959 (2005).

[0005] U.S. Patent No. 4,315,007 ("the '007 patent"), herein incorporated by reference, discloses a process for preparing alfuzosin hydrochloride. In general, the process of the '007 patent includes (a) reacting 4-amino-2-chloro-6,7-dimethoxyquinazoline with methylaminopropionitrile to produce N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine, (b) hydrogenating the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine with Raney nickel; and (c) converting the hydrogenated amine to a hydrochloride salt to provide a N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine hydrochloride intermediate. This intermediate is further reacted with tetrahydrofuroic acid to produce alfuzosin hydrochloride. One problem associated with this process is the formation of the hydrochloride salt of the intermediate leads to the undesired result of having impurities in the final product.

[0006] U.S. Patent No. 5,545,738 ("the '738 patent"), herein incorporated by reference, discloses a process for preparing alfuzosin hydrochloride dihydrate. In general, the process of the '738 patent includes crystallizing anhydrous alfuzosin hydrochloride in a mixture of acetone:water (4:1) to provide alfuzosin hydrochloride dihydrate. The '738 patent further discloses anhydrous, dehydrate, trihydrate and tetrahydrate crystalline forms of alfuzosin hydrochloride.

[0007] Accordingly, there remains a need for an improved process for preparing substantially pure alfuzosin and its salt, alfuzosin hydrochloride.

[0008] Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as

different solubility profiles, different melting point temperatures and/or different x-ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predicable solubility profiles. It is desirable to investigate all solid state forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry. Additionally, polymorphic forms of the same drug substance or active pharmaceutical ingredient, can be administered by itself or formulated as a drug product (also known as the final or finished dosage form), and are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability and compressibility of drug substances and the safety and efficacy of drug products.

[0009] The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It also adds to the material that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. New polymorphic forms of alfuzosin and alfuzosin hydrochloride have now been discovered.

SUMMARY OF THE INVENTION

[0010] In accordance with one embodiment of the present invention, a process for the preparation of alfuzosin and, optionally, a pharmaceutically salt thereof is provided comprising the steps of:

(a) reacting 4-amino-2-chloro-6,7-dimethoxyquinazoline with methylaminopropionitrile to provide N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine;

(b) catalytically hydrogenating the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine to obtain N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine;

(c) reacting the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine with a solution comprising tetrahydrofuroic acid in the presence of thionyl chloride to provide alfuzosin;

(d) recovering the product alfuzosin; and, optionally,

(e) reacting alfuzosin with a suitable mineral acid to obtain a pharmaceutically acceptable salt of alfuzosin.

[0011] In accordance with a second embodiment of the present invention, a process for the preparation of alfuzosin substantially in polymorph Form A is provided comprising the steps of:

(a) reacting N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine with tetrahydrofuroic acid to provide alfuzosin; and

(b) crystallizing alfuzosin in a solvent to provide the alfuzosin substantially in the polymorph Form A.

[0012] In accordance with a third embodiment of the present invention, alfuzosin substantially in polymorph Form A is provided.

[0013] In accordance with a fourth embodiment of the present invention, alfuzosin substantially in the polymorph Form A and having a powder X-ray diffraction (XRD) pattern substantially in accordance with Figure 1 is provided.

[0014] In accordance with a fifth embodiment of the present invention, alfuzosin substantially in the polymorph Form A and exhibiting characteristic peaks (expressed in degrees 2θ ± 0.2°θ) at approximately one or more of the positions: 10.03, 11.11, 12.21, 22.97, 23.16, 23.29 and 24.64.

[0015] In accordance with a sixth embodiment of the present invention, alfuzosin substantially in the polymorph Form A and characterized by having at least one of the following properties is provided:

(a) a melting point in the range of about 182°C to about 184°C;

(b) a powder X-ray diffraction (XRD) pattern substantially in accordance with Figure 1; and/or

(c) a powder XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 1 below:

TABLE 1

Relative Intensity (%)	Angle (2θ)
11.33	8.78
53.59	10.03
48.29	11.11
44.36	12.21
25.23	12.82
31.39	14.95
16.95	17.66
38.16	18.33
23.91	19.34
25.62	19.55
33.63	20.18
30.90	22.60
60.38	22.97
100.00	23.16
77.49	23.29
23.62	23.50
21.93	24.16
53.33	24.64

(d) an Infra-Red (IR) spectrum substantially in accordance with Figure 2; and/or

(e) a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 3.

[0016] In accordance with a seventh embodiment of the present invention, a process for preparing alfuzosin substantially in polymorph Form A is provided comprising (a) crystallizing alfuzosin in a water soluble alcohol having 1 to 4 carbon atoms; and (b) isolating alfuzosin substantially in polymorph Form A.

[0017] In accordance with an eighth embodiment of the present invention, a process for preparing alfuzosin hydrochloride is provided comprising the steps of:

(a) reacting N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine with tetrahydrofuroic acid to provide alfuzosin;

(b) crystallizing alfuzosin in a solvent to provide alfuzosin substantially in polymorph Form A; and

(c) reacting the alfuzosin substantially in polymorph Form A with a hydrochloric acid-containing material to provide alfuzosin hydrochloride.

[0018] In accordance with a ninth embodiment of the present invention, substantially pure alfuzosin hydrochloride is provided.

[0019] In accordance with a tenth embodiment of the present invention, a pharmaceutical composition is provided comprising an active ingredient comprising alfuzosin substantially in polymorph Form A or a pharmaceutically acceptable salt thereof.

[0020] In accordance with an eleventh embodiment of the present invention, a process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph Form I is provided comprising the steps of:

(a) forming a suspension of alfuzosin in a solution comprising a ketone and a hydrochloric acid-containing material; and

(b) recovering the hydrochloride salt of alfuzosin substantially in polymorph Form I from the suspension.

[0021] In accordance with a twelfth embodiment of the present invention, a process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph Form II is provided comprising the steps of:

(a) forming a suspension of alfuzosin in a solution comprising a halogenated hydrocarbon, a lower alcohol and a hydrochloric acid-containing material; and

(b) recovering the hydrochloride salt of alfuzosin substantially in polymorph Form II from the suspension.

[0022] In accordance with a thirteenth embodiment of the present invention, a process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph Form I is provided comprising the steps of:

(a) forming a suspension of a substantially pure alfuzosin substantially in polymorph Form A in a solution comprising a ketone and a hydrochloric acid-containing material; and

(d) recovering the hydrochloride salt of alfuzosin substantially in polymorph Form I from the suspension.

[0023] In accordance with a fourteenth embodiment of the present invention, a process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph Form II is provided comprising the steps of:

(a) forming a suspension of a substantially pure alfuzosin substantially in polymorph Form A in a solution comprising a halogenated hydrocarbon, a lower alcohol and a hydrochloric acid-containing material; and

(b) recovering the hydrochloride salt of alfuzosin substantially in polymorph Form II from the suspension.

[0024] In accordance with a fifteenth embodiment of the present invention, a hydrochloride salt of alfuzosin substantially in polymorph Form I is provided.

[0025] In accordance with a sixteenth embodiment of the present invention, a hydrochloride salt of alfuzosin substantially in polymorph Form I is provided and exhibiting an XRD pattern having characteristic peaks (expressed in degrees $2\theta \pm 0.2°\theta$) at approximately one or more of the positions: 6.94, 8.40, 9.57, 9.76, 10.26, 10.58, 13.30, 13.71, 14.17, 15.09, 17.02, 17.88, 18.90, 19.59, 20.56, 20.91, 21.48, 23.06, 23.37, 24.33, 24.87, 25.30, 26.22, 27.67, 29.17, and 29.78 and/or by the powder XRD pattern substantially in accordance with Figure 4.

[0026] In accordance with a seventeenth embodiment of the present invention, alfuzosin hydrochloride substantially in the polymorph Form I and characterized by having at least one of the following properties is provided:

(a) a powder XRD pattern substantially in accordance with Figure 4;

(b) a powder XRD pattern comprising characteristic peaks (expressed in degrees $2\theta \pm 0.2°\theta$) summarized in Table 2 below:

TABLE 2

Relative Intensity (%)	Angle (2θ)
65.63	6.94
17.13	8.40
15.78	9.57
22.52	9.76
44.08	10.26
100.00	10.58
32.17	13.30
18.18	13.71
18.63	14.17
12.73	15.09
23.26	17.02
18.27	17.88
15.89	18.90
37.54	19.59
75.80	20.56
55.49	20.91
16.47	21.48
21.69	23.06
25.68	23.37
88.30	24.33
63.84	24.87
60.90	25.30
47.64	26.22
21.06	27.67
65.55	29.17
18.25	29.78

(c) an IR spectrum substantially in accordance with Figure 5; and/or

(d) a DSC thermogram substantially in accordance with Figure 6.

[0027] In accordance with an eighteenth embodiment of the present invention, a hydrochloride salt of alfuzosin substantially in polymorph Form II is provided.

[0028] In accordance with a nineteenth embodiment of the present invention, a hydrochloride salt of alfuzosin substantially in polymorph Form II is provided and exhibiting an XRD pattern having characteristic peaks (expressed in degrees 2θ ± 0.2°θ) at approximately one or more of the positions: 3.02, 5.81, 7.13, 8.68, 9.39, 10.45, 10.80, 11.44, 11.51, 13.50, 14.28, 17.14, 20.26, 20.77, 21.07, 24.47, 25.04, 25.57, 26.28, 29.28, and 44.61 and/or by the powder XRD pattern substantially in accordance with Figure 7.

[0029] In accordance with a twentieth embodiment of the present invention, alfuzosin hydrochloride substantially in the polymorph Form II and characterized by having at least one of the following properties is provided:

(a) an XRD pattern substantially in accordance with Figure 7;

(b) an XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 3 below:

TABLE 3

Relative Intensity (%)	Angle (2θ)
100	3.02
89.52	5.81
64.76	7.13
58.61	8.68
26.10	9.39
18.14	10.45
33.36	10.80
37.67	11.44
32.45	11.51
16.00	13.50
17.87	14.28
18.94	17.14
25.70	20.26
22.83	20.77
15.99	21.07
28.66	24.47
21.66	25.04
43.69	25.57
33.78	26.28
18.91	29.28
23.40	44.61

(c) an IR spectrum substantially in accordance with Figure 8; and/or

(d) a DSC thermogram substantially in accordance with Figure 9.

[0030] In accordance with a twenty-first embodiment of the present invention, a substantially pure hydrochloride salt of alfuzosin substantially in polymorph Form I or II is provided.

[0031] In accordance with a twenty-second embodiment of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of an active pharmaceutical ingredient comprising alfuzosin substantially in polymorph Form A.

[0032] In other embodiments of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of an active pharmaceutical ingredient comprising a hydrochloride salt of alfuzosin substantially in polymorph Forms I and/or II.

DEFINITIONS

[0033] The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

[0034] The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0035] The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host means causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by topical, local or by systemic administration of the active ingredient to the host.

[0036] As used herein, the term "buffering agent" is intended to mean a compound used to resist a change in pH upon dilution or addition of acid of alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate and other such material known to those of ordinary skill in the art.

[0037] As used herein, the term "sweetening agent" is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

[0038] As used herein, the term "binders" is intended to mean substances used to cause adhesion of powder particles in tablet granulations. Such compounds include, by way of example and without limitation, acacia alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch, combinations thereof and other material known to those of ordinary skill in the art.

[0039] When needed, other binders may also be included in the present invention. Exemplary binders include starch, poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC™ F68, PLURONIC™ F127), collagen, albumin, celluloses in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone), combinations thereof and other such materials known to those of ordinary skill in the art.

[0040] As used herein, the term "diluent" or "filler" is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate,

sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.

[0041] As used herein, the term "glidant" is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

[0042] As used herein, the term "lubricant" is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the art.

[0043] As used herein, the term "disintegrant" is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starched thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose (e.g. Avicel™), carsium (e.g. Amberlite™), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof and other such materials known to those of ordinary skill in the art.

[0044] As used herein, the term "wetting agent" is intended to mean a compound used to aid in attaining intimate contact between solid particles and liquids. Exemplary wetting agents include, by way of example and without limitation, gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, (e.g., TWEEN™s), polyethylene glycols, polyoxyethylene stearates colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose,

hydroxyl propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton) is another useful wetting agent, combinations thereof and other such materials known to those of ordinary skill in the art.

[0045] Most of these excipients are described in detail in, e.g., Howard C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, (7th Ed. 1999); Alfonso R. Gennaro et al., Remington: The Science and Practice of Pharmacy, (20th Ed. 2000); and A. Kibbe, Handbook of Pharmaceutical Excipients, (3rd Ed. 2000), which are incorporated by reference herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0046] Figure 1 is a characteristic X-ray powder diffraction pattern of polymorph Form A of alfuzosin.

[0047] Figure 2 is a characteristic Infra-Red (IR) spectrum of polymorph Form A of alfuzosin.

[0048] Figure 3 is a characteristic differential scanning calorimetric (DSC) thermogram of polymorph Form A of alfuzosin.

[0049] Figure 4 is a characteristic XRD pattern of polymorph Form I of alfuzosin hydrochloride.

[0050] Figure 5 is a characteristic IR spectrum of polymorph Form I of alfuzosin hydrochloride.

[0051] Figure 6 is a characteristic differential scanning calorimetric (DSC) thermogram of polymorph Form I of alfuzosin hydrochloride.

[0052] Figure 7 is a characteristic X-ray powder diffraction pattern of polymorph Form II of alfuzosin hydrochloride.

[0053] Figure 8 is a characteristic IR spectrum of polymorph Form II of alfuzosin hydrochloride.

[0054] Figure 9 is a characteristic differential scanning calorimetric (DSC) thermogram of polymorph Form II of alfuzosin hydrochloride.

[0055] Figure 10 is a characteristic X-ray powder diffraction pattern of an anhydrous crystalline form of alfuzosin hydrochloride prepared by the process of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0056] The present invention is directed to a process of preparing alfuzosin and pharmaceutically acceptable salts thereof. In one embodiment of the present invention, a process for preparing alfuzosin or a pharmaceutically acceptable salt thereof includes at least:

[0057] (a) reacting 4-amino-2-chloro-6,7-dimethoxyquinazoline (Formula II) with methylaminopropionitrile to provide N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine (Formula III);

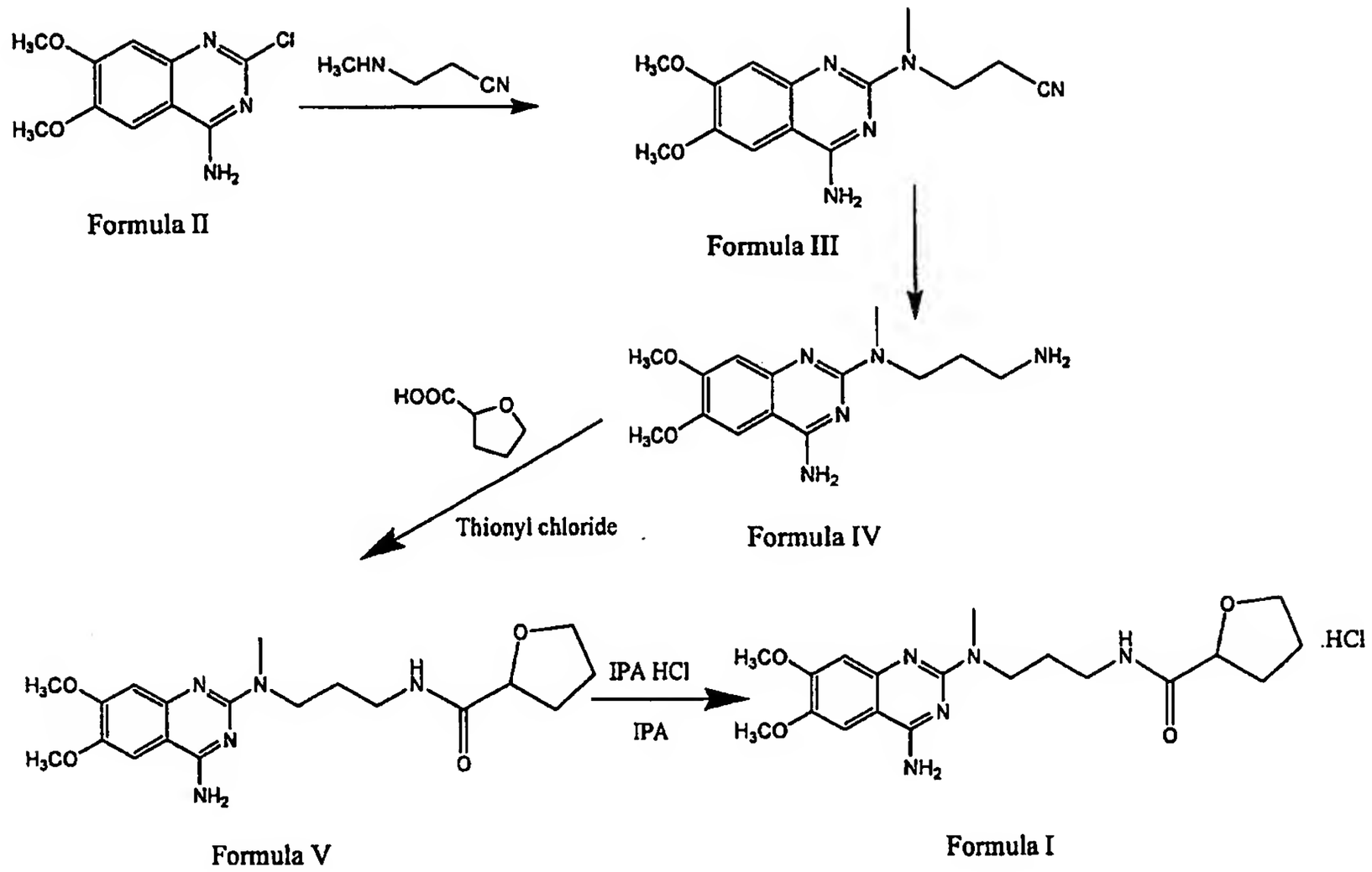
[0058] (b) catalytically hydrogenating the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine (Formula III) to provide N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine (Formula IV);

[0059] (c) reacting the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine (Formula IV) with tetrahydrofuroic acid;

[0060] (d) recovering the alfuzosin (Formula V) (e.g., by isolation followed by crystallization from a solvent); and optionally

[0061] (e) reacting alfuzosin with a mineral acid to provide a pharmaceutically acceptable salt of alfuzosin (Formula I). This process is generally depicted in Scheme 1 below:

Scheme I



[0062] In step (a) of this process of the present invention, 4-amino-2-chloro-6,7-dimethoxyquinazoline is reacted with methylaminopropionitrile in a suitable solvent to obtain N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine. Useful solvents include alcohols, e.g., methanol, ethanol, isopropyl alcohol, isoamyl alcohol and the like. The reaction can be carried out at a temperature ranging from about 100°C to about 150°C and preferably for about 135°C to about 140°C. The time period for the reaction can range from about 2 hour to about 10 hours and preferably from about 3 hours to about 6 hours. If desired, following completion of the reaction, the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine thus obtained can be purified utilizing ethanol/water.

[0063] In step (b) of this process of the present invention, N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine is catalytically hydrogenated to provide N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine. For example, the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine can be catalytically hydrogenated in the presence of an unsupported or supported catalyst,

e.g., rhodium catalyst on an alumina support, Raney nickel, palladium on charcoal and the like. The temperature of this reaction will ordinarily range from about 25°C to about 50°C. The reaction can also be carried out under a pressure ranging from about 10 kg to about 70 kg and preferably from about 10 kg to about 30 kg.

[0064] In step (c) of this process of the present invention, N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine is condensed by reaction with tetrahydrofuroic acid in the presence of a suitable coupling agent, e.g., thionyl chloride. By using thionyl chloride in this step, tetrahydrofuroic acid chloride is generated in situ. This reaction may be advantageously carried out in at least one solvent and in the presence of a coupling agent. Useful coupling agents include, but are not limited to, N,N'-carbonyl diimidazole, alkyl chloroformates, such as ethyl chloroformate, isobutyl chloroformate, benzyl chloroformate, dicyclohexyl carbodiimide and the like and mixtures thereof.. Useful solvents include haloalkanes, e.g., dichloromethane, carbon tetrachloride, chloroform, 1,2-dichloroethane and the like; ethers, e.g., tetrahydrofuran, diisopropyl ether, diethyl ether and the like and mixtures thereof. The preferred solvent for this step is tetrahydrofuran. The reaction temperature may range from about 40°C to about 100°C, preferably from about 65°C to about 70°C. The reaction time may vary from about 1 hour to about 5 hours, and preferably from about 1.5 hours to about 2.5 hours.

[0065] The alfuzosin thus obtained is ordinarily in a solid form, e.g., a gummy form. The resulting alfuzosin may be extracted using a water immiscible solvent, for example, esters, such as ethyl acetate, isopropyl acetate, isobutyl acetate, or haloalkanes, such as, dichloromethane, 1,2-dichloroethane, chloroform and the like and mixtures thereof. The water immiscible solvent is preferably dichloromethane. Following the extraction of alfuzosin, the solvent may then be distilled. The distillation temperature varies from a temperature ranging from about 30°C to about 60°C, and preferably from about 40°C to about 45°C.

[0066] In step (d) of this process of the present invention, alfuzosin is recovered. For example, alfuzosin can be isolated by adding a solvent such as an ester, e.g., ethyl acetate, isopropyl acetate, isobutyl acetate and the like; alcohol, e.g., methanol, ethyl alcohol, isopropyl alcohol and the like and mixtures thereof. The preferred solvent for isolation is ethyl acetate, methanol and ethanol. The isolation temperature varies from

about 5°C to about 40°C and preferably from about 15°C to about 20°C for a time period ranging from about 1 hour to about 6 hours, and preferably from about 2 hours to about 3 hours. The isolated alfuzosin may be purified by standard techniques known to those skilled in this art, e.g., crystallization in esters, alcohols, hydrocarbons, preferably alcohols such as methanol, ethanol, isopropyl alcohol, and the like and most preferably isopropyl alcohol to provide pure alfuzosin.

[0067] In step (e) of this process of the present invention, the alfuzosin thus obtained may optionally be reacted with a suitable mineral acid to obtain a pharmaceutically acceptable salt of alfuzosin. For example, to obtain the hydrochloride salt of alfuzosin, the alfuzosin of step (d) can be reacted with a hydrochloric acid-containing material such as, for example, hydrochloric acid, alcoholic hydrochloric acid or hydrochloric acid gas, and preferably alcoholic hydrochloric acids. Useful alcohols may be methanol, ethanol, isopropyl alcohol, n-butanol, t-butanol and the like, and preferably methanol and ethanol. The concentration of the hydrochloric acid-containing material varies from about 5% to about 15%, and preferably from about 5% to about 10%. The temperature of the reaction varies from about 15°C to about 50°C, preferably from about 20°C to about 30°C. The pharmaceutically acceptable salt of alfuzosin is preferably the hydrochloride salt.

[0068] Another aspect of the present invention is directed to a process for preparing alfuzosin substantially in polymorph Form A, which is a particularly useful intermediate in preparing pharmaceutically acceptable salts thereof, e.g., alfuzosin hydrochloride and polymorphs thereof. Crystallinity of the novel polymorphs of this invention may be measured using methods familiar to those skilled in the art. The novel polymorphs of the present invention as described hereinbelow were characterized by X-ray powder diffraction (XRD), IR analysis and differential scanning calorimetry. The X-Ray powder diffraction spectrum for each of the novel polymorphs, i.e., Forms A, I and II, were measured by an X-ray powder Diffractometer equipped with a Cu-anode (λ=1.54 Angstrom), X-ray source operated at 45kV, 40 mA and a Ni filter is used to strip K-beta radiation. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=2-50° 2θ; step width=0.017°; and measuring time per step=5 sec.

[0069] The Infra-Red ("IR") spectrum of polymorph Form A of alfuzosin and Forms I and II of alfuzosin hydrochloride were obtained on a Perkin Elmer FT-IR spectrometer. The sample was prepared by KBr powder technique registering the spectrum on reflectance.

[0070] Measurements of differential scanning calorimetry ("DSC") for polymorph Form A of alfuzosin and Forms I and II of alfuzosin hydrochloride were obtained on a differential scanning calorimeter.

[0071] Generally, the process for preparing alfuzosin substantially in polymorph Form A of the present invention includes at least:

(a) reacting N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylene diamine with tetrahydrofuroic acid to provide alfuzosin; and

(b) crystallizing alfuzosin in a solvent to provide alfuzosin in substantially polymorph Form A.

[0072] In step (a) of this process of the present invention, the reaction of N-(4-amino-6,7-dimethoxyquinazolin-2-yl)-N-methylpropanediamine with tetrahydrofuroic acid to obtain alfuzosin can be carried out as described hereinabove.

[0073] In step (b) of this process of the present invention, alfuzosin is crystallized in a solvent to obtain alfuzosin substantially in polymorphic Form A. It may be advantageous prior to the step of crystallizing to first isolate alfuzosin by adding a solvent under an elevated temperature followed by purification. The solvent may be, for example, esters such as ethyl acetate, isopropyl acetate, isobutyl acetate and the like, alcohols such as methanol, ethyl alcohol, isopropyl alcohol and the like and mixtures thereof. Preferably, the solvent is ethyl acetate and/or methanol. The solution is heated to a temperature ranging from about 40°C to about 60°C, and preferably from about 55°C to about 60°C. The solution may be heated for about 1 to about 6 hours and preferably from about 2 to about 3 hours. Alfuzosin can then be isolated, for example, by filtration, washed and then dried.

[0074] Suitable solvents for crystallizing alfuzosin include esters, alcohols and hydrocarbons, e.g., aliphatic, aromatic and/or halogenated hydrocarbons. Preferably, crystallization is carried out in one or more alcohols such as, for example, methanol, ethanol, isopropyl alcohol, and most preferably in isopropyl alcohol. Crystallization is

carried out by first suspending alfuzosin in a solvent at a temperature ranging from about 40°C to about 60°Cfor about 20 minutes to about 1 hour. Next, the suspension is cooled to room temperature and isolated by conventional techniques, e.g., filtration, to obtain alfuzosin substantially in polymorph Form A. If desired, the isolated product can then be washed, e.g., with an alcohol such as isopropyl alcohol, and dried. The substantially polymorphic Form A of alfuzosin may then be purified by conventional techniques known to those skilled in this art, e.g., crystallization. The purity of the alfuzosin substantially in polymorph Form A can be greater than about 99.5%. Accordingly, in one embodiment of the present invention, substantially pure alfuzosin is provided.

[0075] The alfuzosin substantially in polymorphic Form A of the present invention exhibits characteristic peaks (expressed in degrees 2θ ± 0.2°θ) at approximately one or more of the positions: 10.03, 11.11, 12.21, 22.97, 23.16, 23.29 and 24.64. In general, the alfuzosin substantially in the polymorph Form A can be characterized by having at least one, and preferably all, of the following properties:

(a) a melting point in the range of about 182°C to about 184°C;

(b) a powder X-ray diffraction (XRD) pattern substantially in accordance with Figure 1; and/or

(c) a powder XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 1 below:

TABLE 1

Relative Intensity (%)	Angle (2θ)
11.33	8.78
53.59	10.03
48.29	11.11
44.36	12.21
25.23	12.82
31.39	14.95
16.95	17.66
38.16	18.33
23.91	19.34
25.62	19.55
33.63	20.18
30.90	22.60
60.38	22.97
100.00	23.16
77.49	23.29
23.62	23.50
21.93	24.16
53.33	24.64

(d) an Infra-Red (IR) spectrum substantially in accordance with Figure 2; and/or

(e) a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 3.

[0076] Another aspect of the present invention is directed to crystalline Forms I and II of hydrochloride salts of alfuzosin. In one embodiment, a hydrochloride salt of alfuzosin substantially in polymorph Form I is provided and can be characterized by having at least one, and preferably all, of the following properties:

(a) a powder XRD pattern substantially in accordance with Figure 4;

(b) a powder XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 2 below:

TABLE 2

Relative Intensity (%)	Angle (2θ)
65.63	6.94
17.13	8.40
15.78	9.57
22.52	9.76
44.08	10.26
100.00	10.58
32.17	13.30
18.18	13.71
18.63	14.17
12.73	15.09
23.26	17.02
18.27	17.88
15.89	18.90
37.54	19.59
75.80	20.56
55.49	20.91
16.47	21.48
21.69	23.06
25.68	23.37
88.30	24.33
63.84	24.87
60.90	25.30
47.64	26.22
21.06	27.67
65.55	29.17
18.25	29.78

(c) an IR spectrum substantially in accordance with Figure 5; and/or

(d) a DSC thermogram substantially in accordance with Figure 6.

[0077] Generally, a hydrochloride salt of alfuzosin substantially in polymorph Form I can be obtained by first forming a suspension of alfuzosin or alfuzosin substantially in polymorph Form A in a mixture comprising a ketone and hydrochloric acid-containing material; and then separating the hydrochloride salt of alfuzosin substantially in polymorph Form I from the suspension. Alfuzosin is known and can be formed by known techniques or those described above.

[0078] In step (a) of the process for preparing a hydrochloride salt of alfuzosin substantially in polymorph Form I of the present invention, the foregoing alfuzosin or alfuzosin substantially in polymorph Form A can be added to a mixture containing at least one or more ketones, and a hydrochloric acid-containing material. Suitable ketones can have from 1 to about 20 carbon atoms, and include, but are not limited to, acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, methyl isopropyl ketone, ethyl propyl ketone, ethyl isopropyl ketone, dipropyl ketone, diisopropyl ketone, methyl butyl ketone, methyl isobutyl ketone and the like. Suitable hydrochloric acid-containing material can be, for example, concentrated hydrochloric acid, alcoholic hydrochloric acid, hydrochloric acid gas, and the like and preferably alcoholic hydrochloric acids. The alcohol of the alcoholic hydrochloric acids may be methanol, ethanol, isopropyl alcohol, n-butanol, t-butanol and the like, and preferably methanol and/or isopropyl alcohol. The concentration of hydrochloric acid in an alcohol solution varies from about 5 to about 15%, and preferably from about 5 to about 10% by weight, based on the total weight of the solution. The reaction may be performed at a temperature ranging from about 15°C to about 50°C, and preferably from about 25°C to about 30°C. In one embodiment, a mixture of hydrochloric acid and acetone is added to the suspension until a pH of about 1.5 to about 5 is obtained. If desired, the suspension can then be stirred at room temperature for about one hour.

[0079] The product can then be separated from the suspension by, for example, filtration, and washed with a suitable solvent, e.g., a ketone such as acetone. The wet product can be dried at a temperature of about 50°C to about 55°C to obtain substantially pure alfuzosin hydrochloride substantially in polymorph Form I. In one embodiment, the process provides anhydrous polymorph Form I of alfuzosin hydrochloride.

[0080] In another embodiment of the present invention, a hydrochloride salt of alfuzosin substantially in polymorph Form II is provided and can be characterized by having at least one, and preferably all, of the following properties:

(a) a powder XRD pattern substantially in accordance with Figure 7;

(b) a powder XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 3 below:

TABLE 3

Relative Intensity (%)	Angle (2θ)
100	3.02
89.52	5.81
64.76	7.13
58.61	8.68
26.10	9.39
18.14	10.45
33.36	10.80
37.67	11.44
32.45	11.51
16.00	13.50
17.87	14.28
18.94	17.14
25.70	20.26
22.83	20.77
15.99	21.07
28.66	24.47
21.66	25.04
43.69	25.57
33.78	26.28
18.91	29.28
23.40	44.61

(c) an IR spectrum substantially in accordance with Figure 8; and/or

(d) a DSC thermogram substantially in accordance with Figure 9.

[0081] Generally, a hydrochloride salt of alfuzosin substantially in polymorph Form II can be obtained by first forming a suspension of the foregoing alfuzosin or alfuzosin substantially in polymorph Form A in a mixture containing at least a halogenated hydrocarbon, a lower alcohol and a hydrochloric acid-containing material. Suitable halogenated hydrocarbons include, but are not limited to, dichloromethane, carbon tetrachloride, chloroform, 1,2-dichloroethane and the like and mixtures thereof. Suitable alcohols may be selected from the group consisting of ethanol, isopropyl alcohol, n-butanol, t-butanol and the like and mixtures thereof. The hydrochloric acid-containing material can be any of the foregoing hydrochloric acid-containing material. In one embodiment, a mixture of hydrochloric acid and isopropyl alcohol can be added to the

suspension until a pH of about 1.5 is obtained. The suspension may then be stirred at room temperature for about 10 to about 12 hours.

[0082] The product can then be separated from the suspension by, for example, filtration, and washed with a suitable solvent, e.g., a halogenated hydrocarbon such as dichloromethane. The wet product can be dried at a temperature of about 50°C to about 55°C to obtain pure alfuzosin hydrochloride substantially in polymorph Form II. In one embodiment, the process provides anhydrous polymorph Form II of alfuzosin hydrochloride.

[0083] Yet another aspect of the present invention is directed to crystalline alfuzosin hydrochloride substantially in anhydrous form. Crystalline alfuzosin hydrochloride substantially in anhydrous form may be prepared by forming a suspension of alfuzosin or alfuzosin substantially in polymorph Form A in a mixture containing at least an acetate, a lower alcohol and a hydrochloric acid-containing material. Alfuzosin for use in this embodiment is known and can be formed by known techniques or those described above. Suitable acetates include, but are not limited to, methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, butyl acetate and the like and mixtures thereof. Suitable alcohols may be selected from the group consisting of methanol, ethanol, isopropyl alcohol, n-butanol, t-butanol and the like and mixtures thereof. The hydrochloric acid-containing material may be any of the foregoing hydrochloric acid-containing material. In one embodiment, a mixture of hydrochloric acid and methanol may be added to the suspension until a pH of about 1.5 to about 5 is obtained. The suspension may then be stirred at room temperature for about 3 to about 12 hours. The product may then be separated from the suspension by, for example, filtration, and washed with a suitable solvent, e.g., acetates such as ethyl acetate. The wet product may be dried at a temperature ranging from about 45°C to about 60°C, preferably from about 50°C to about 55°C, to obtain pure alfuzosin hydrochloride substantially in anhydrous polymorph.

[0084] The product can then be separated from the suspension by, for example, filtration, and washed with a suitable solvent, e.g., acetates such as ethyl acetate. The wet product can be dried at a temperature of about 50°C to about 55°C to obtain substantially pure alfuzosin hydrochloride substantially in anhydrous crystalline forms.

[0085] Yet another aspect of the present invention is directed to pharmaceutical compositions containing at least the novel polymorphic forms of alfuzosin disclosed herein. Such pharmaceutical compositions may be administered to a mammalian patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include, but are not limited to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The novel polymorphic forms of alfuzosin disclosed herein also may be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes. The dosage forms may contain the novel polymorphic forms of alfuzosin disclosed herein as is or, alternatively, may contain the novel polymorphic forms of alfuzosin disclosed herein as part of a composition. The pharmaceutical compositions may further contain one or more pharmaceutically acceptable excipients. Suitable excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field, e.g., the buffering agents, sweetening agents, binders, diluents, fillers, lubricants, wetting agents and disintegrants described hereinabove.

[0086] Capsule dosages will contain the novel polymorphic forms of alfuzosin disclosed herein within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxy methyl ethyl cellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

[0087] Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, the compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl

cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

[0088] Other excipients contemplated by the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

[0089] In one embodiment, the novel polymorphic forms of alfuzosin disclosed herein for use in the pharmaceutical compositions of the present invention can have a D_{50} and D_{90} particle size of less than about 400 microns, preferably less than about 200 microns, more preferably less than about 150 microns, still more preferably less than about 50 microns and most preferably less than about 15 microns. The particle sizes of the novel polymorphic forms of alfuzosin can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the solid state polymorphic forms of alfuzosin into any of the foregoing desired particle size range.

[0090] Actual dosage levels of the alfuzosin of the invention may be varied to obtain an amount of alfuzosin that is effective to obtain a desired therapeutic response for a particular composition and method of administration for treatment of a mammal. The selected dosage level therefore depends upon such factors as, for example, the desired therapeutic effect, the route of administration, the desired duration of treatment, and other factors. The total daily dose of the alfuzosin of this invention administered to a host in single or divided dose and can vary widely depending upon a variety of factors including, for example, the body weight, general health, sex, diet, time and route of administration,

rates of absorption and excretion, combination with other drugs, the severity of the particular condition being treated, etc.

[0091] The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the claims.

EXAMPLE 1

[0092] Preparation of N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine

[0093] 4-amino-2-chloro-6,7-dimethoxyquinazoline (200.0 g) and methylaminopropionitrile (84.20 g) were charged in isoamyl alcohol (1400.0 ml) and heated to reflux a temperature ranging from about 135°C to about 140°C for 4 hours. Reaction completion is checked by Thin Layer Chromatography ("TLC"). After completion of the reaction as determined by TLC, mass is cooled, filtered and dried. The dried material is then crystallized form aqueous ethanol to get N-(4-amino-6, 7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine (185.0 g, 78.0% yield). HPLC purity > 96 %

EXAMPLE 2

[0094] Preparation of N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine

[0095] N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine (185.0 g) obtained from Example 1 is hydrogenated (30kg pressure) in methanol by using rhodium on alumina (9.25 g) at a temperature ranging from about 45°C to about 50°C for 6 hours. The reaction mass was then filtered and concentrated. Acetonitrile is then charged and heated to reflux for 30 minutes. The reaction mass is then filtered and dried to get N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylene diamine (139.0 g, 74.0% yield). Purity > 85%

EXAMPLE 3

[0096] Preparation of Alfuzosin

[0097] A solution of tetrahydrofuroic acid (47.80 g) and N,N'-carbonyl diimidazole (66.78 g) in tetrahydrofuran (1000.0 ml) stirred for about 30 to about 35 minutes at a temperature ranging from about 40°C to about 45°C under nitrogen atmosphere. N-(4-amino-6,7-dimethoxyquinaaolin-2-yl)-N-methylpropylenediamine (100.0 g) was charged to the reaction mass and continued reaction at reflux temperature for about 90 to about 105 minutes. The reaction was monitored by TLC (methanol: ethyl acetate - 8:2). On completion of the reaction as determined by TLC, the reaction mass was cooled to a temperature ranging from about 40°C to about 45°C and the solvent was evaporated at a temperature ranging from about 40°C to about 45°C under vacuum. Sodium hydroxide (1000.0 ml, 2N) was added to the reaction mass, extracted the mass with dichloromethane (2 X 500 ml), dried over sodium sulfate and concentrated to dryness to obtain gummy mass. To the gummy mass, ethyl acetate (1000.0 ml) was charged and heated to a temperature ranging from about 55°C to about 60°C and stirred at the same temperature for about 30 to about 35 minutes. The mass was cooled to room temperature. The product was isolated by filtration, washed with ethyl acetate (100.0 ml). Wet product was dried at a temperature ranging from about 50°C to about 55°C to obtained crude alfuzosin.

[0098] The crude product was suspended in isopropyl alcohol (1000 ml), at a temperature ranging from about 50°C to about 55°C for about 30 to about 35 minutes. The suspension was cooled to room temperature. The product was isolated by filtration, washed with isopropyl alcohol (100 ml). The wet product was dried at a temperature ranging from about 50°C to about 55°C to obtain pure alfuzosin (112.0 g, 84% yield), substantially free from impurities.

[0099] Purity (by HPLC): Greater than 99.5%

[00100] Moisture content: 0.01%

[00101] IR(cm^{-1}): 3412, 3343, 3244, 3086, 2988, 2936, 2877, 1649, 1567, 1502, 1473, 1439, 1402, 1384, 1344, 1284, 1259, 1238, 1208, 1053.

[00102] Melting Range: 182.2°C to 183.8°C

[00103] H^1 NMR: δ 8.63 (1H,s), 6.98 (1H,s), 6.82 (1H,s), 5.84 (2H,s), 4.51-4.46 (1H,dd), 4.1-3.9 (10H,m), 3.62-3.54 (1H,m), 3.4-3.33 (1H,m), 3.16 (3H,s), 3-2.86 (1H,m), 2.33-2.2 (2H,m), 2-1.17 (3H,m), 1.64-1.55 (1H,m)

[00104] MASS [(M+H)+]: 390.1

EXAMPLE 4

[00105] Preparation of Alfuzosin

[00106] A solution of tetrahydrofuroic acid (47.80 g) and N,N'-carbonyl diimidazole (66.78 g) in dichloromethane ("MDC") (1000.0 ml) stirred for about 30 to about 35 minutes at a temperature ranging from about 40°C to about 42°C under nitrogen atmosphere. N-(4-amino-6,7-dimethoxyquinazolin-2-yl)-N-methylpropylenediamine (100.0 g) to reaction mass and continued reaction at reflux temperature for about 90 to about 105 minutes. The reaction was monitored by TLC (methanol:ethyl acetate - 8:2). On completion of the reaction mass as determined by TLC, the reaction mass was cooled to a temperature ranging from about 20°C to about 25°C and added to 2N sodium hydroxide (1000 ml) solution, stirred for 30 minutes and separated the MDC layer. MDC layer was then dried over sodium sulfate and concentrated to dryness to obtain gummy mass. Ethanol (300.0 ml) was charged to the gummy mass and heated to a temperature ranging from about 55°C to about 60°C and stirred at same temperature for about 30 for about 35 minutes. The mass was cooled to room temperature. The product was isolated by filtration, washed with ethanol (100.0 ml). The wet product was dried at a temperature ranging from about 50°C to about 55°C to obtained crude alfuzosin.

[00107] The crude product was suspended in methanol (1000 ml), at a temperature ranging from about 50°C to about 55°C for about 30 to about 35 minutes. The suspension was cooled to room temperature. The product was isolated by filtration, washing with methanol (100 ml). The wet product was dried at a temperature ranging from about 50°C to about 55°C to obtained pure alfuzosin (112.0 g, 84% yield), free from impurities.

[00108] Purity(by HPLC): Greater than 99.6%

[00109] IR (cm^{-1}): 3412, 3343, 3244, 3086, 2988, 2936, 2877, 1649, 1567, 1502, 1473, 1439, 1402, 1384, 1344, 1284, 1259, 1238, 1208, 1053.

[00110] Melting Range: 182.2°C to 183.8°C

[00111] H^1 NMR: δ 8.63 (1H,s), 6.98 (1H,s), 6.82 (1H,s), 5.84 (2H,s), 4.51-4.46 (1H,dd), 4.1-3.9 (10H,m), 3.62-3.54 (1H,m), 3.4-3.33 (1H,m), 3.16 (3H,s), 3-2.86 (1H,m), 2.33-2.2 (2H,m), 2-1.17 (3H,m), 1.64-1.55 (1H,m).

[00112] MASS [(M+H)+]: 390.1

EXAMPLE 5

[00113] Preparation of Alfuzosin

[00114] To a solution of tetrahydrofuroic acid (5.97 g) in methylene chloride (100 ml) was added thionyl chloride (3.75 ml). After 30 minutes of stirring, N-(4-amino-6,7-dimethoxy-2-quinaaolinyl)-N-methyl-1,3-propanediamine (10.0 g) was added and charged to the reaction mass. To this reaction mass was added triethyl amine, and maintained for about 90 minutes to about 105 minutes. On completion of the reaction as determined by TLC, the reaction mass was filtered to separate the insoluble triethylamine ("TEA") hydrochloride and the solvent was evaporated at a temperature ranging from about 40°C to about 45°C under vacuum, to obtain gummy mass. To the gummy mass, isopropyl alcohol (50 ml) was charged and heated to a temperature ranging from about 55°C to about 60°C and stirred at the same temperature for about 30 to about 35 minutes. The mass was cooled to room temperature. The product was isolated by filtration, washed with isopropyl alcohol (10.0 ml). Wet product was dried at a temperature ranging from about 50°C to about 55°C to obtained crude alfuzosin (7.8gm).

[00115] Purity(by HPLC): Greater than 99.6%

EXAMPLE 6

[00116] Preparation of Polymorph Form A of Alfuzosin

[00117] A solution of tetrahydrofuroic acid (11.26 g, 0.0969 mol) and N,N'-carbonyl diimidazole (15.72 g, 0.0969 mol) in tetrahydrofuran (300 ml) was stirred for 30 to 35 minutes at a temperature of 40°C to 45°C under a nitrogen atmosphere. N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine (25 g, 0.0858 mol) was charged to the reaction mass and the reaction was continued at reflux for 90 to 105 minutes. The reaction was monitored by thin layer chromatography (TLC) (methanol: ethyl acetate - 8:2). On completion of the reaction as determined by TLC, the reaction mixture was

cooled to a temperature of 40°C to 45°C and then the solvent was evaporated at a temperature of 40°C to 45°C under vacuum to provide a residue. To the residue, 2N sodium hydroxide (250 ml) was added, the mass was extracted with dichloromethane (2X250 ml), dried over sodium sulfate and concentrated to dryness to obtain a gummy mass.

[00118] Ethyl acetate (250 ml) was charged to the gummy mass and heated to a temperature of 55°C to 60°C and stirred 30 to 35 minutes. The mass was cooled to room temperature. The product was isolated by filtration, washed with ethyl acetate (25 ml). The wet product was dried at a temperature of 50°C to 55°C to obtain crude alfuzosin.

[00119] The crude product was suspended in isopropyl alcohol (10 volumes), at a temperature of 50°C to 55°C for 30 to 35 minutes. The suspension was cooled to room temperature. The product was isolated by filtration, washed with isopropyl alcohol (1 volume). The wet product was dried at a temperature of 50°C to 55°C to obtain pure alfuzosin substantially in polymorph A form (28 g, 84% yield).

Purity (by HPLC):> 99.5%

IR (cm^{-1}): 3412, 3343, 3244, 3086, 2988, 2936, 2877, 1649, 1567, 1502, 1473, 1439, 1402, 1384, 1344, 1284, 1259, 1238, 1208, 1053 etc.

Melting Range: 182.0°C to 184.0°C

H^1 NMR: δ8.63 (1H,s), 6.98 (1H,s), 6.82 (1H,s), 5.84 (2H,s), 4.51-4.46 (1H,dd), 4.1-3.9 (10H,m), 3.62-3.54 (1H,m), 3.4-3.33 (1H,m), 3.16(3H,s), 3-2.86 (1H,m), 2.33-2.2 (2H,m), 2-1.17 (3H,m), 1.64-1.55 (1H,m)

MASS $[(M^+H)^+]$: 390.1

[00120] The average values of diffraction angles and the relative intensities in the powder X-ray diffraction spectrum of alfuzosin substantially in polymorph form A are given above in Table 1. The XRD, IR and DSC of the final product are set forth in Figures 1-3 and were recorded and identified as polymorph Form A form of alfuzosin.

EXAMPLE 7

[00121] Preparation of Alfuzosin Hydrochloride

[00122] Alfuzosin (50.0 g) was suspended in isopropyl alcohol (500.0 ml). Hydrochloric acid in isopropyl alcohol (5-10%, 100.0 ml) was added to the suspension at

room temperature. The suspension was stirred at the same temperature for about 45 to about 60 minutes. The product was isolated by filtration, washed with isopropyl alcohol (50 ml). The wet product was dried at a temperature ranging from about 50°C to about 55°C to obtained pure alfuzosin hydrochloride. (45 g, 82% yield)

[00123] Purity (by HPLC): Greater than 99.6%

EXAMPLE 8

[00124] Preparation of Alfuzosin Hydrochloride

[00125] Alfuzosin (50 g) was suspended in a mixture of ethanol (200.0 ml) and methanol (50 ml). Hydrochloric acid in isopropyl alcohol (5-10%, 100 ml) was added to the suspension at room temperature. The suspension was stirred at same temperature for about 45 to about 60 minutes. The product was isolated by filtration, washed with ethanol (50 ml). The wet product was dried at a temperature ranging from about 50°C to about 55°C to obtained pure alfuzosin hydrochloride. (45 g, 82% yield)

[00126] Purity (by HPLC): Greater than 99.6%

EXAMPLE 9

[00127] Preparation of Alfuzosin Hydrochloride

[00128] Alfuzosin (10 g) obtained in Example 5 was suspended in isopropyl alcohol (10 volumes). Hydrochloric acid in isopropyl alcohol (5-6%, 2.5 volumes) was added at room temperature. The suspension was stirred at room temperature for 45 to 60 minutes. The product was isolated by filtration, washed with isopropyl alcohol (1 volume). The wet product was dried at a temperature of 50°C to 55°C to obtain alfuzosin hydrochloride (9 g, 82% yield).

Purity (by HPLC): > 99.6%

EXAMPLE 10

[00129] Preparation of Crystalline Form I of Alfuzosin Hydrochloride

[00130] Alfuzosin (3.0 g) obtained in Example 5 was suspended in acetone (10 volumes). A solution of acetone in hydrochloric acid was added to the suspension at room temperature until a pH of about 1.5 was obtained. The suspension was stirred at room

temperature for 45 to 60 minutes. The product was isolated by filtration, and washed with acetone (1 volume). The wet product was dried at a temperature of 50°C to 55°C to obtain pure alfuzosin hydrochloride substantially in polymorph form I (2.7 g).

[00131] Purity (by HPLC): > 99.6%

[00132] The average values of diffraction angles and the relative intensities in the powder X-ray diffraction spectrum of alfuzosin hydrochloride substantially in polymorph Form I are given above in Table 2. The XRD, IR and DSC of the final product are set forth in Figures 4-6 and were recorded and identified as polymorph Form I of alfuzosin hydrochloride.

EXAMPLE 11

[00133] Preparation of Crystalline Form II of Alfuzosin Hydrochloride

[00134] Alfuzosin (3.0 g) obtained in Example 5 was suspended in dichloromethane (10 volumes). Hydrochloric acid (5-6%) in isopropyl alcohol (5-6%, 2.5 volumes) was added to the suspension at room temperature until a pH of 1.5 was obtained. The suspension was stirred at room temperature for 10 to 12 hours. The product was isolated by filtration, and washed with dichloromethane (1 volume). The wet product was dried at a temperature of 50-55°C to obtain pure alfuzosin hydrochloride substantially in polymorph form II (2.60 g).

Purity (by HPLC): > 99.6%

[00135] The average values of diffraction angles and the relative intensities in the powder X-ray diffraction spectrum of alfuzosin hydrochloride substantially in polymorph form II are given above in Table 3. The XRD, IR and DSC of the final product are set forth in Figures 7-9 and were recorded and identified as polymorph Form I of alfuzosin hydrochloride.

EXAMPLE 12

[00136] Preparation of Alfuzosin Hydrochloride Anhydrous Polymorph

[00137] Alfuzosin (50 g) was suspended in a mixture of ethyl acetate (250 ml) and isopropyl acetate (250 ml). Hydrochloric acid in methanol (5-10%, 150 ml) was added to the suspension at room temperature. The suspension was stirred at the same temperature

for about 3 to about 5 hours at 20-25°C. The product was isolated by filtration, washed with ethyl acetate (100 ml). The wet product was dried at a temperature ranging from about 50°C to about 55°C to obtain the desired anhydrous polymorph of pure alfuzosin hydrochloride (45 g, 82% yield).

[00138] Purity (by HPLC): Greater than 99.6%

[00139] The XRD of the final product is set forth in Figure 10 and was recorded and identified as anhydrous polymorph of alfuzosin hydrochloride.

[00140] While the above description contains many specifics, these specifics should not be construed as limitations of the invention, but merely as exemplifications of preferred embodiments thereof. Those skilled in the art will envision many other embodiments within the scope and spirit of the invention as defined by the claims appended hereto.

WHAT IS CLAIMED IS:

1. Alfuzosin substantially in polymorph Form A and characterized by having at least one of the following properties:

(a) a melting point in the range of about 182°C to about 184°C;

(b) a powder X-ray diffraction (PXRD) pattern substantially in accordance with Figure 1; and/or

(c) a PXRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 1 below.

TABLE 1:

Relative Intensity (%)	Angle (2θ)
11.33	8.78
53.59	10.03
48.29	11.11
44.36	12.21
25.23	12.82
31.39	14.95
16.95	17.66
38.16	18.33
23.91	19.34
25.62	19.55
33.63	20.18
30.90	22.60
60.38	22.97
100.00	23.16
77.49	23.29
23.62	23.50
21.93	24.16
53.33	24.64

(d) an Infra-Red (IR) spectrum substantially in accordance with Figure 2; and/or

(e) a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 3.

2. A process for the preparation of alfuzosin substantially in polymorphic Form A comprising:

(a) reacting N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine with tetrahydrofuroic acid to provide alfuzosin; and

(b) crystallizing alfuzosin in a solvent to provide the alfuzosin substantially in the polymorph Form A.

3. The process of Claim 2, further comprising

reacting 4-amino-2-chloro-6,7-dimethoxyquinazoline with methylaminopropionitrile to provide a N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine;

catalytically hydrogenating the N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methyl-2-cyanoethyl amine to provide N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine.

reacting N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine with tetrahydrofuroic acid to provide alfuzosin; and

crystallizing the alfuzosin in a first solvent to provide alfuzosin substantially in polymorph Form A.

4. The process of Claim 3, wherein the reaction of N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine with tetrahydrofuroic acid is carried out in a second solvent and in the presence of a coupling agent.

5. The process of Claim 4, wherein the second solvent is selected from the group consisting of haloalkanes, ethers and mixtures thereof. and the coupling agent is selected from the group consisting of N,N'-carbonyl diimidazole, alkyl chloroformates, dicyclohexyl carbodiimide, thionyl chloride and mixtures thereof.

6. The process of Claim 4, wherein the second solvent is tetrahydrofuran and the coupling agent is N,N'-carbonyl diimidazole.

7. The process of Claims 2-6, wherein in step (b) the solvent is isopropyl alcohol.

8. The process of Claims 2-7, wherein the alfuzosin substantially in the polymorph A form possesses a purity of greater than about 99.5%.

9. The process of Claims 2-8, further comprising the step of converting the alfuzosin substantially in polymorph Form A to a pharmaceutically acceptable salt thereof.

10. The process of Claim 2-9, wherein the alfuzosin substantially in polymorph Form A is reacted with a mineral acid.

11. The process of Claim 10, wherein the mineral acid is a hydrochloric acid.

12. Alfuzosin substantially in polymorphic Form A prepared by the process of Claims 2-11.

13. A pharmaceutical composition comprising a therapeutically effective amount of an active pharmaceutical ingredient comprising the alfuzosin substantially in polymorphic Form A of Claims 1 and 12 and one or more pharmaceutically acceptable excipients.

14. The pharmaceutical composition of Claim 13, wherein the alfuzosin substantially in polymorphic Form A is a micronized alfuzosin substantially in polymorphic Form A or a pharmaceutically acceptable salt thereof having a particle size of less than about 400 microns.

15. The pharmaceutical composition of Claim 13, wherein the alfuzosin substantially in polymorphic Form A is a micronized alfuzosin substantially in polymorphic Form A or a pharmaceutically acceptable salt thereof having a particle size of less than about 200 microns.

16. The pharmaceutical composition of Claim 13, wherein the alfuzosin substantially in polymorphic Form A is a micronized alfuzosin substantially in polymorphic Form A or a pharmaceutically acceptable salt thereof having a particle size of less than about 150 microns.

17. The pharmaceutical composition of Claim 13, wherein the alfuzosin substantially in polymorphic Form A is a micronized alfuzosin substantially in polymorphic Form A or a pharmaceutically acceptable salt thereof having a particle size of less than about 50 microns.

18. The pharmaceutical composition of Claim 13, wherein the alfuzosin is a micronized alfuzosin or a pharmaceutically acceptable salt thereof having a particle size of less than about 15 microns.

19. A process for preparing alfuzosin hydrochloride comprising the steps of:

(a) reacting N-(4-amino-6,7-dimethoxyquinazol-2-yl)-N-methylpropylenediamine with tetrahydrofuroic acid to provide alfuzosin;

(b) crystallizing alfuzosin in a solvent to provide alfuzosin substantially in polymorph Form A; and

(c) reacting the alfuzosin substantially in polymorph Form A with a hydrochloric acid-containing material to provide alfuzosin hydrochloride.

20. Substantially pure alfuzosin hydrochloride.

21. Alfuzosin hydrochloride having a purity greater than or equal to about 99%.

22. Alfuzosin hydrochloride having a purity greater than or equal to about 99.5%.

23. Alfuzosin hydrochloride substantially in polymorph Form I and characterized by having at least one of the following properties:

(a) a powder XRD pattern substantially in accordance with Figure 4;

(b) a powder XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 2 below:

TABLE 2

Relative Intensity (%)	Angle (2θ)
65.63	6.94
17.13	8.40
15.78	9.57
22.52	9.76
44.08	10.26
100.00	10.58
32.17	13.30
18.18	13.71
18.63	14.17
12.73	15.09
23.26	17.02
18.27	17.88
15.89	18.90
37.54	19.59
75.80	20.56
55.49	20.91
16.47	21.48
21.69	23.06
25.68	23.37
88.30	24.33
63.84	24.87
60.90	25.30
47.64	26.22
21.06	27.67
65.55	29.17
18.25	29.78

(c) an IR spectrum substantially in accordance with Figure 5; and/or

(d) a DSC thermogram substantially in accordance with Figure 6.

24. The alfuzosin hydrochloride substantially in polymorph Form I of Claim 23, which is in anhydrous form.

25. A pharmaceutical composition comprising a therapeutically effective amount of an active pharmaceutical ingredient comprising the alfuzosin hydrochloride substantially in polymorph Form I of Claims 23 and 24 and one or more pharmaceutically acceptable excipients.

26. The pharmaceutical composition of Claim 25, wherein the alfuzosin hydrochloride substantially in polymorph Form I is a micronized alfuzosin hydrochloride substantially in polymorph Form I having a particle size of less than about 400 microns.

27. The pharmaceutical composition of Claim 25, wherein the alfuzosin hydrochloride substantially in polymorph Form I is a micronized alfuzosin hydrochloride substantially in polymorph Form I having a particle size of less than about 200 microns.

28. The pharmaceutical composition of Claim 25, wherein the alfuzosin hydrochloride substantially in polymorph Form I is a micronized alfuzosin hydrochloride substantially in polymorph Form I having a particle size of less than about 150 microns.

29. The pharmaceutical composition of Claim 25, wherein the alfuzosin hydrochloride substantially in polymorph Form I is a micronized alfuzosin hydrochloride substantially in polymorph Form I having a particle size of less than about 50 microns.

30. The pharmaceutical composition of Claim 25, wherein the alfuzosin hydrochloride substantially in polymorph Form I is a micronized alfuzosin hydrochloride substantially in polymorph Form I having a particle size of less than about 15 microns.

31. A process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph form I, the process comprising:

(a) forming a suspension of alfuzosin in a mixture comprising a ketone and a hydrochloric acid-containing material; and

(b) separating the hydrochloride salt of alfuzosin substantially in polymorph form I from the suspension.

32. The process of Claim 31, wherein the hydrochloric acid-containing material is a concentrated hydrochloric acid, an alcoholic hydrochloric acid or a hydrochloric acid gas.

33. The process of Claims 31 and 32, wherein the ketone contains from 1 to about 20 carbon atoms.

34. The process of Claims 31-33, wherein the ketone is selected from the group consisting of acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, methyl isopropyl ketone, ethyl propyl ketone, ethyl isopropyl ketone, dipropyl ketone, diisopropyl ketone, methyl butyl ketone, methyl isobutyl ketone and mixtures thereof.

35. The process of Claims 31-34, wherein the ketone is acetone and the hydrochloric acid-containing material is a concentrated hydrochloric acid.

36. The process of Claims 31-35, wherein the hydrochloride salt of alfuzosin substantially in polymorph Form I obtained possesses a purity of greater than or equal to about 99.5%.

37. A process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph Form I, the process comprising the steps of:

(a) forming a suspension of a substantially pure alfuzosin substantially in polymorph Form A in a solution comprising a ketone and a hydrochloric acid-containing material; and

(d) recovering the hydrochloride salt of alfuzosin substantially in polymorph Form I from the suspension.

38. The process of Claim 37, wherein the hydrochloric acid-containing material is a concentrated hydrochloric acid, an alcoholic hydrochloric acid or a hydrochloric acid gas.

39. The process of Claims 37 and 38, wherein the ketone contains from 1 to about 20 carbon atoms.

40. The process of Claims 37-39, wherein the ketone is selected from the group consisting of acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, methyl isopropyl ketone, ethyl propyl ketone, ethyl isopropyl ketone, dipropyl ketone, diisopropyl ketone, methyl butyl ketone, methyl isobutyl ketone and mixtures thereof.

41. The process of Claims 37-40, wherein the ketone is acetone and the hydrochloric acid-containing material is a concentrated hydrochloric acid.

42. Alfuzosin hydrochloride substantially in polymorph Form I prepared by the process of Claims 31-41.

43. Alfuzosin hydrochloride substantially in polymorph Form II and characterized by having at least one of the following properties:

(a) an XRD pattern substantially in accordance with Figure 7;

(b) an XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) summarized in Table 3 below:

TABLE 3

Relative Intensity (%)	Angle (2θ)
100	3.02
89.52	5.81
64.76	7.13
58.61	8.68
26.10	9.39
18.14	10.45
33.36	10.80
37.67	11.44
32.45	11.51
16.00	13.50
17.87	14.28
18.94	17.14
25.70	20.26
22.83	20.77
15.99	21.07
28.66	24.47
21.66	25.04
43.69	25.57
33.78	26.28
18.91	29.28
23.40	44.61

(c) an IR spectrum substantially in accordance with Figure 8; and/or

(d) a DSC thermogram substantially in accordance with Figure 9.

44. The alfuzosin hydrochloride substantially in polymorph Form II of Claim 43, which is in anhydrous form.

45. A pharmaceutical composition comprising a therapeutically effective amount of the alfuzosin hydrochloride substantially in polymorph Form II of Claims 43 and 44 and one or more pharmaceutically acceptable excipients.

46. The pharmaceutical composition of Claim 45, wherein the alfuzosin hydrochloride substantially in polymorph Form II is a micronized alfuzosin hydrochloride substantially in polymorph Form II having a particle size of less than about 400 microns.

47. The pharmaceutical composition of Claim 45, wherein the alfuzosin hydrochloride substantially in polymorph Form II is a micronized alfuzosin hydrochloride substantially in polymorph Form II having a particle size of less than about 200 microns.

48. The pharmaceutical composition of Claim 45, wherein the alfuzosin hydrochloride substantially in polymorph Form II is a micronized alfuzosin hydrochloride substantially in polymorph Form II having a particle size of less than about 150 microns.

49. The pharmaceutical composition of Claim 45, wherein the alfuzosin hydrochloride substantially in polymorph Form II is a micronized alfuzosin hydrochloride substantially in polymorph Form II having a particle size of less than about 50 microns.

50. The pharmaceutical composition of Claim 45, wherein the alfuzosin hydrochloride substantially in polymorph Form II is a micronized alfuzosin hydrochloride substantially in polymorph Form II having a particle size of less than about 15 microns.

51. A process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph Form II, the process comprising:

(a) forming a suspension of alfuzosin in a mixture comprising a halogenated hydrocarbon, a lower alcohol and a hydrochloric acid-containing material; and

(b) recovering the hydrochloride salt of alfuzosin substantially in polymorph Form II from the suspension.

52. The process of Claim 51, wherein the hydrochloric acid-containing material is a concentrated hydrochloric acid, an alcoholic hydrochloric acid or a hydrochloric acid gas.

53. The process of Claims 51 and 52, wherein the halogenated hydrocarbon is selected from the group consisting of dichloromethane, carbon tetrachloride, chloroform, 1,2-dichloroethane and mixtures thereof and the lower alcohol is selected from the group consisting of ethanol, isopropyl alcohol, n-butanol, t-butanol and mixtures thereof.

54. The process of Claims 51-53, wherein the halogenated hydrocarbon is dichloromethane, the lower alcohol is isopropyl alcohol and the hydrochloric acid-containing material is a concentrated hydrochloric acid.

55. The process of Claims 51-54, wherein the hydrochloride salt of alfuzosin substantially in polymorph Form II obtained possesses a purity of greater than or equal to about 99.5%.

56. A process for the preparation of a hydrochloride salt of alfuzosin substantially in polymorph Form II, the process comprising the steps of:

(a) forming a suspension of a substantially pure alfuzosin substantially in polymorph Form A in a solution comprising a halogenated hydrocarbon, a lower alcohol and a hydrochloric acid-containing material; and

(b) recovering the hydrochloride salt of alfuzosin substantially in polymorph Form II from the suspension.

57. The process of Claim 56, wherein the hydrochloric acid-containing material is a concentrated hydrochloric acid, an alcoholic hydrochloric acid or a hydrochloric acid gas.

58. The process of Claims 56 and 57, wherein the halogenated hydrocarbon is selected from the group consisting of dichloromethane, carbon tetrachloride, chloroform, 1,2-dichloroethane and mixtures thereof and the lower alcohol is selected from the group consisting of ethanol, isopropyl alcohol, n-butanol, t-butanol and mixtures thereof.

59. The process of Claims 56-58, wherein the halogenated hydrocarbon is dichloromethane, the lower alcohol is isopropyl alcohol and the hydrochloric acid-containing material is a concentrated hydrochloric acid.

60. The process of Claims 56-59, wherein the hydrochloride salt of alfuzosin substantially in polymorph Form II obtained possesses a purity of greater than or equal to about 99.5%.

61. Alfuzosin hydrochloride substantially in polymorph Form I prepared by the process of Claims 51-60.

62. A substantially pure hydrochloride salt of alfuzosin substantially in polymorph Form I or II.

63. The substantially pure hydrochloride salt of alfuzosin substantially in polymorph Form I or II, having a purity of greater than or equal to about 99.5%.

64. A process for the preparation of a polymorph of alfuzosin hydrochloride substantially in anhydrous form, the process comprising the steps of:

(a) forming a suspension of a substantially pure alfuzosin or substantially pure alfuzosin substantially in polymorph Form A in a solution comprising an acetate, a lower alcohol and a hydrochloric acid-containing material; and

(b) recovering the polymorph of alfuzosin hydrochloride substantially in anhydrous form from the suspension.

65. The process of Claim 64, wherein the acetate is selected from the group consisting of methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, butyl acetate and mixtures thereof.

66. The process of Claims 64 and 65, wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropyl alcohol, n-butanol, t-butanol and mixtures thereof.

67. The process of Claims 64-66, wherein the hydrochloric acid-containing material is a mixture of hydrochloric acid and methanol.

68. Anhydrous crystalline form of alfuzosin hydrochloride, having a particle size of less than about 400 microns.

69. Anhydrous crystalline form of alfuzosin hydrochloride, having a particle size of less than about 200 microns.

70. Anhydrous crystalline form of alfuzosin hydrochloride, having a particle size of less than about 150 microns.

71. Anhydrous crystalline form of alfuzosin hydrochloride, having a particle size of less than about 50 microns.

72. Anhydrous crystalline form of alfuzosin hydrochloride, having a particle size of less than about 15 microns.

73. Anhydrous crystalline forms of alfuzosin hydrochloride prepared by the process of Claims 64-67.

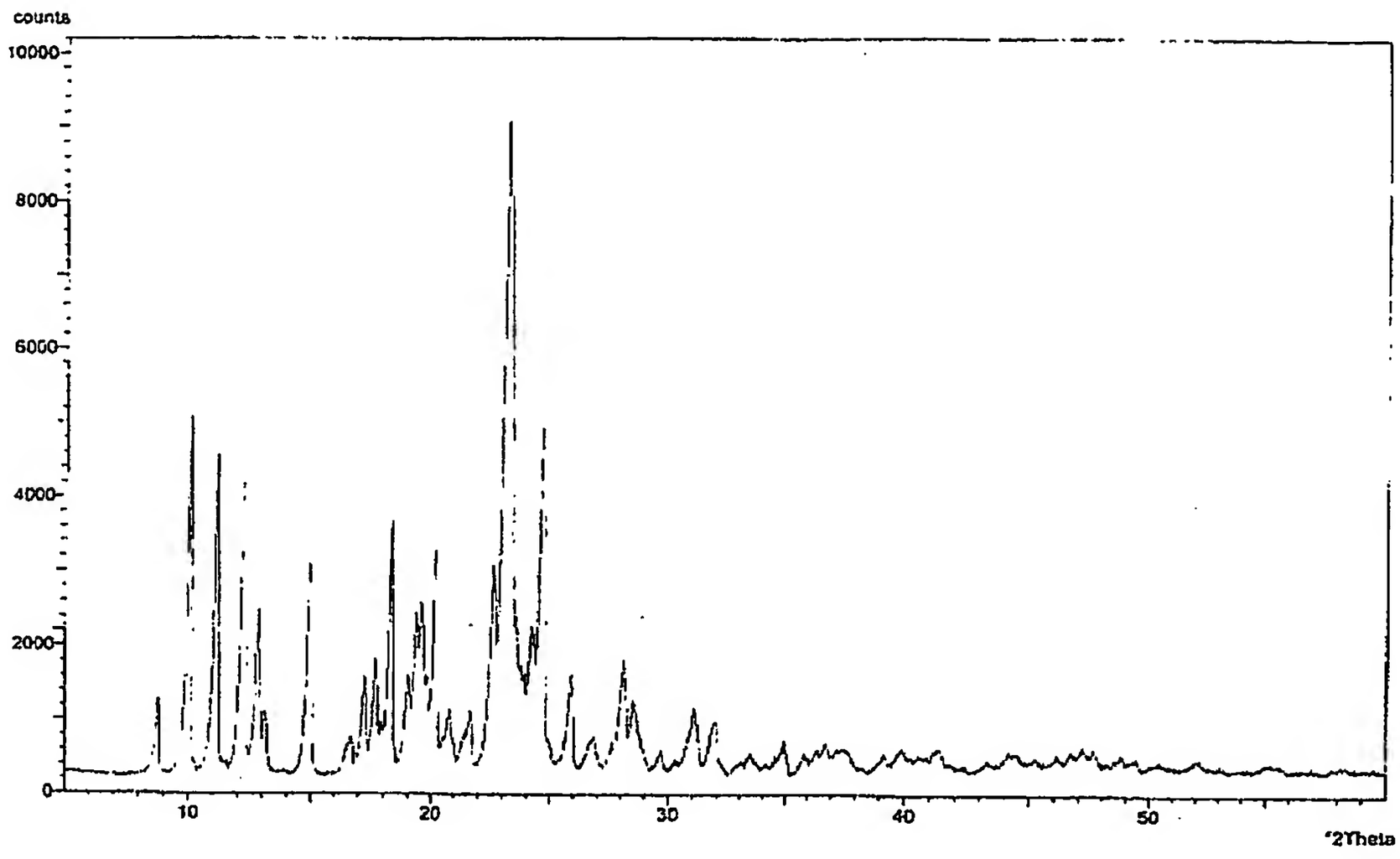


FIGURE 1

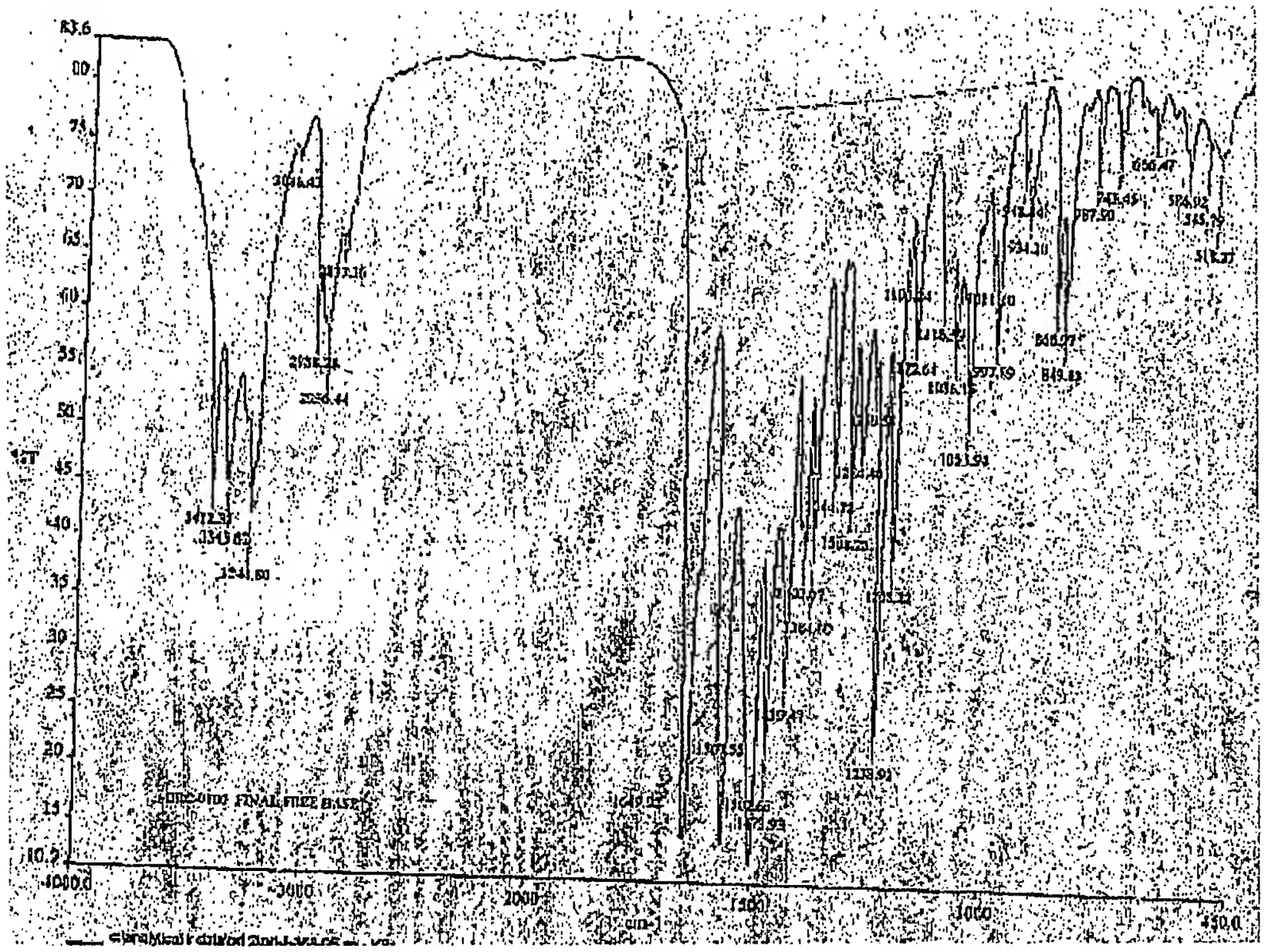


FIGURE 2

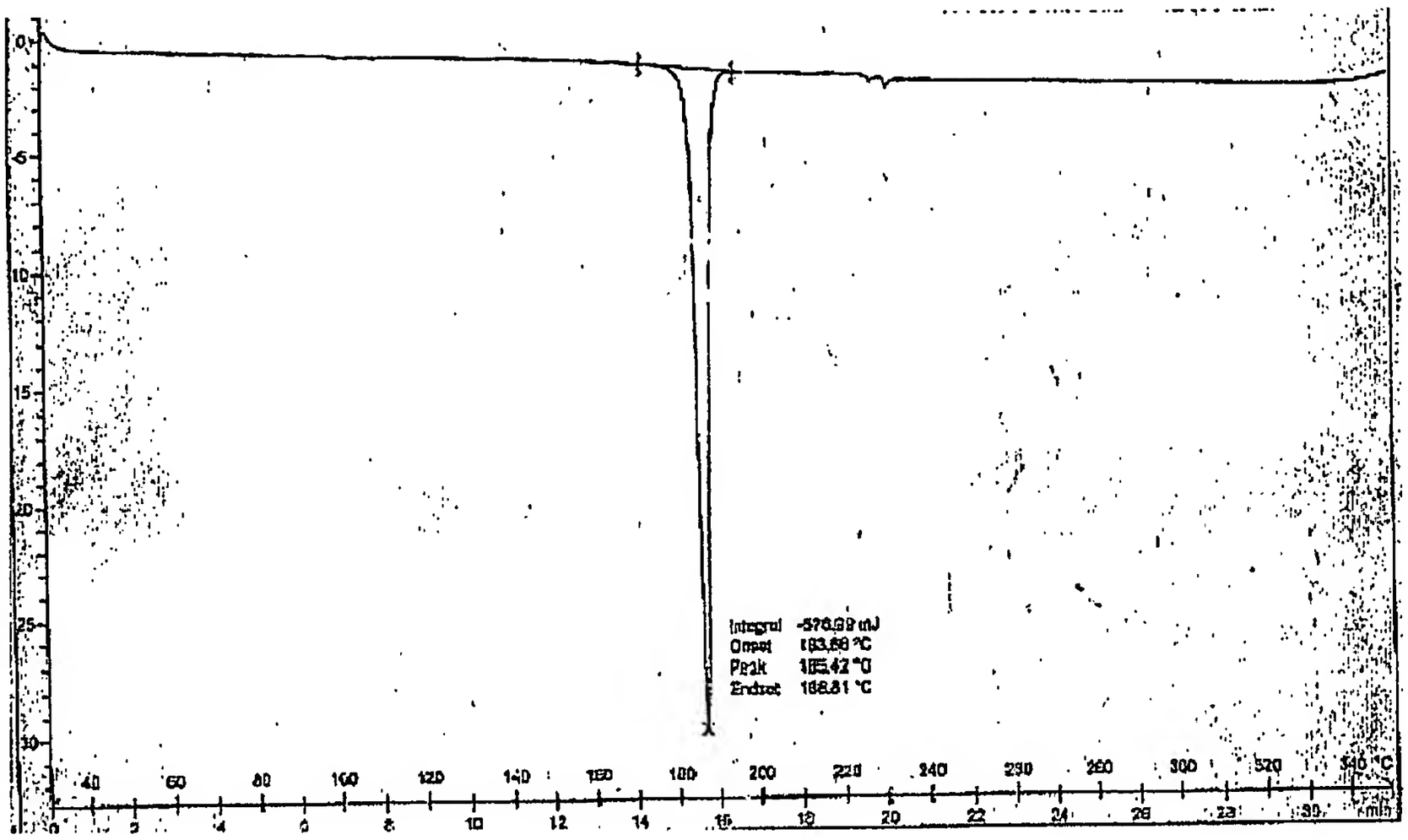

Integral -576.99 mJ
Onset 183.69 °C
Peak 185.42 °C
Endset 188.81 °C
°C
min

FIGURE 3

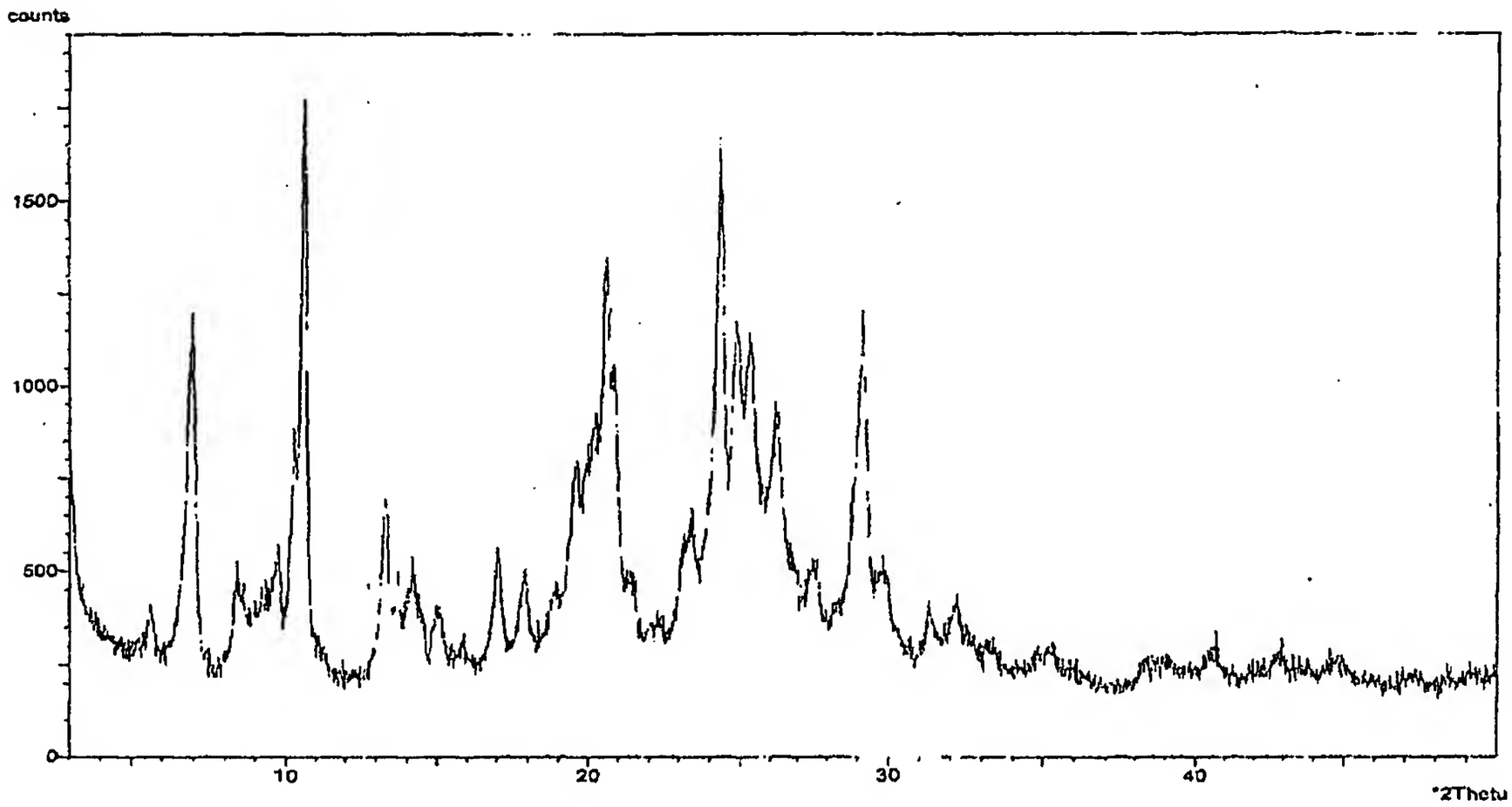


FIGURE 4

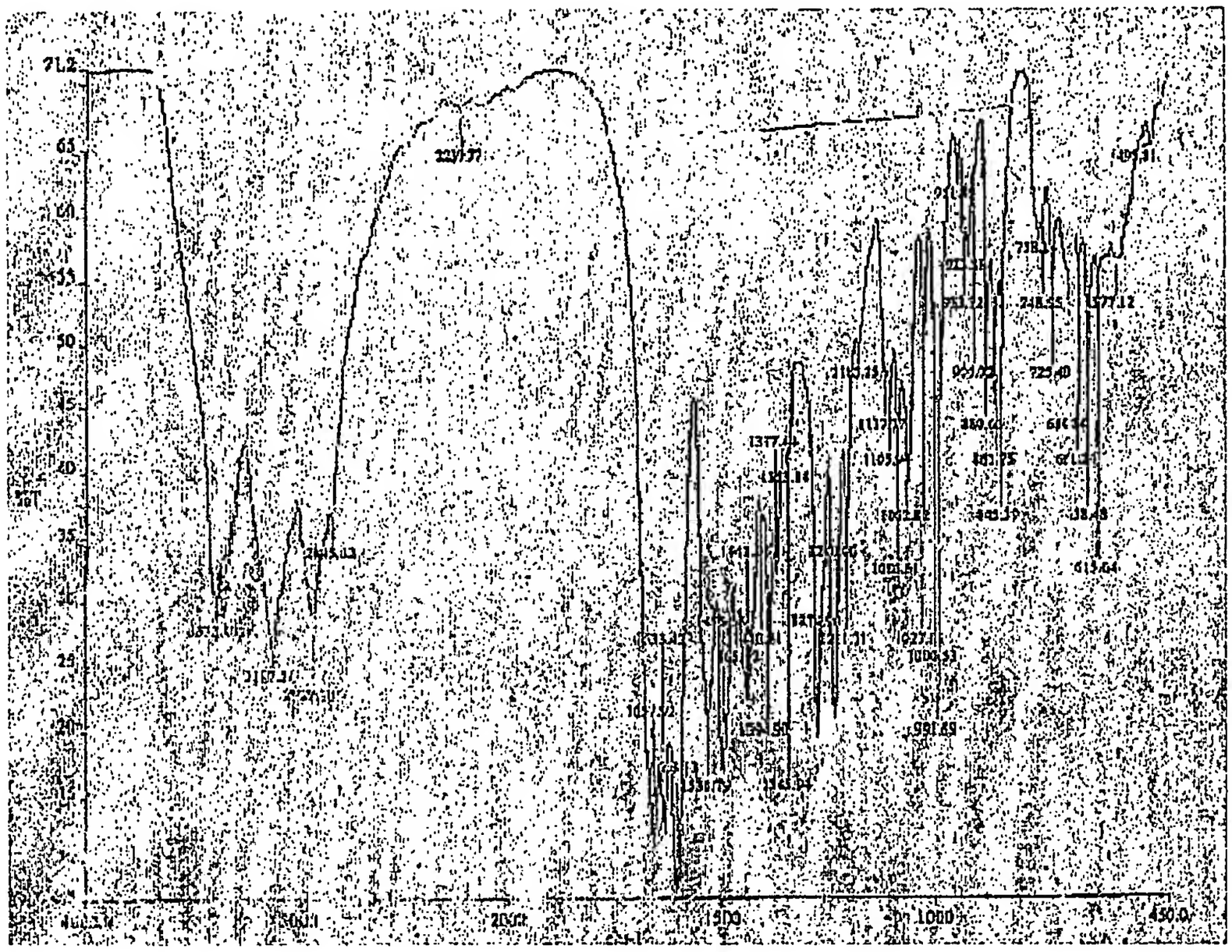


FIGURE 5

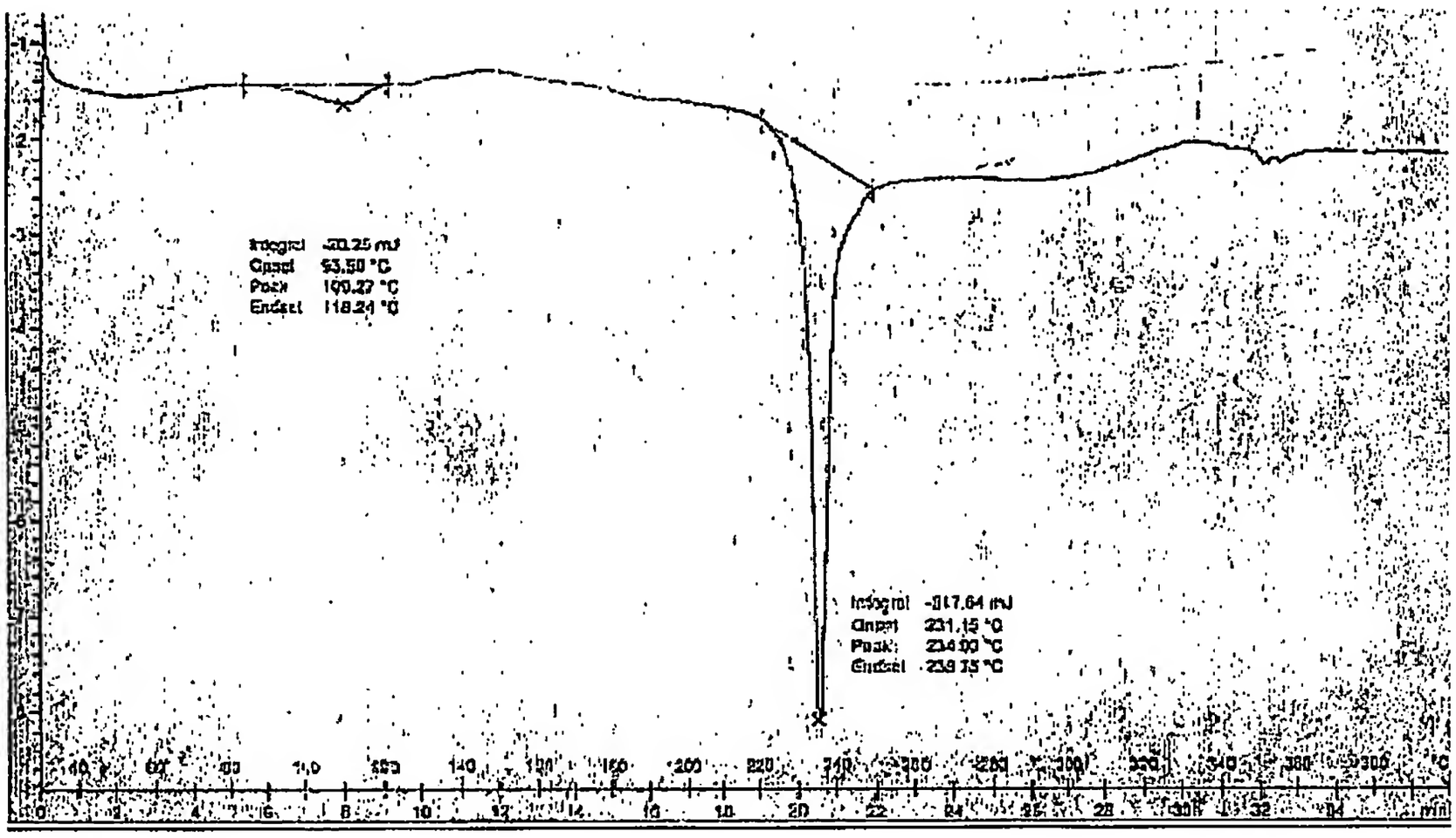

Integral -20.25 mJ
Onset 93.50 °C
Peak 100.27 °C
Endset 118.24 °C
Integral -817.64 mJ
Onset 231.15 °C
Peak 234.00 °C
Endset 239.75 °C
min

FIGURE 6

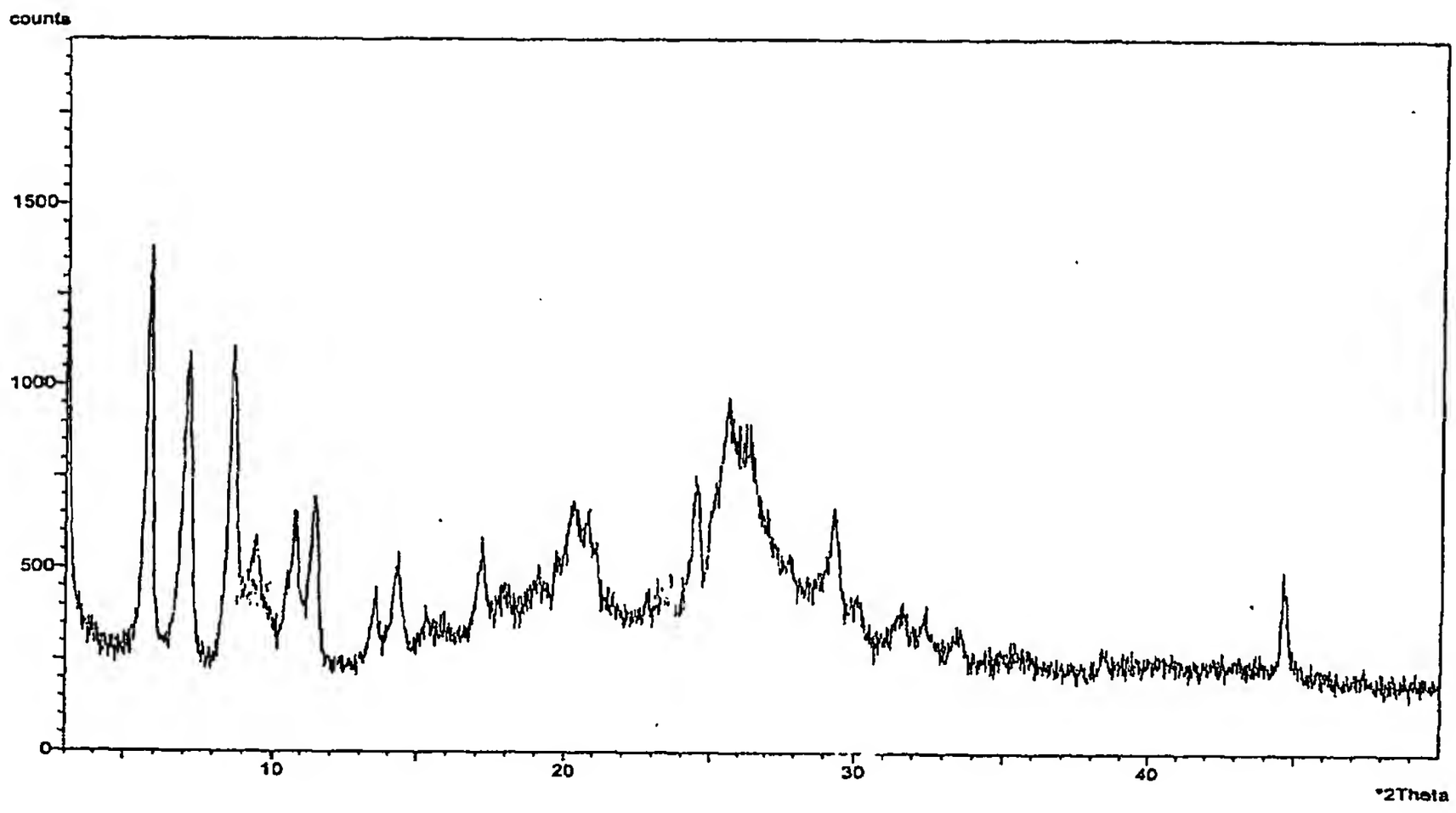


FIGURE 7

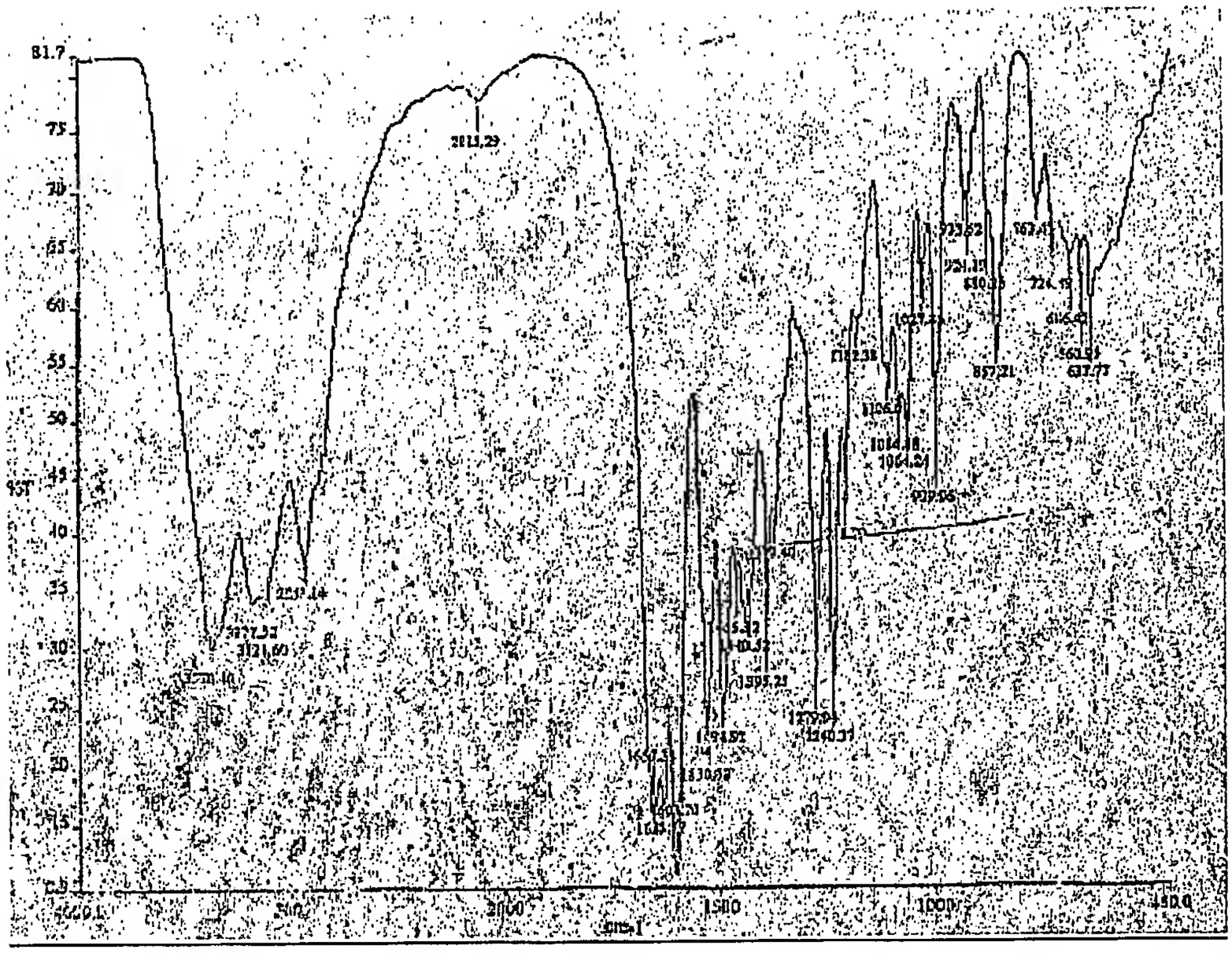


FIGURE 8

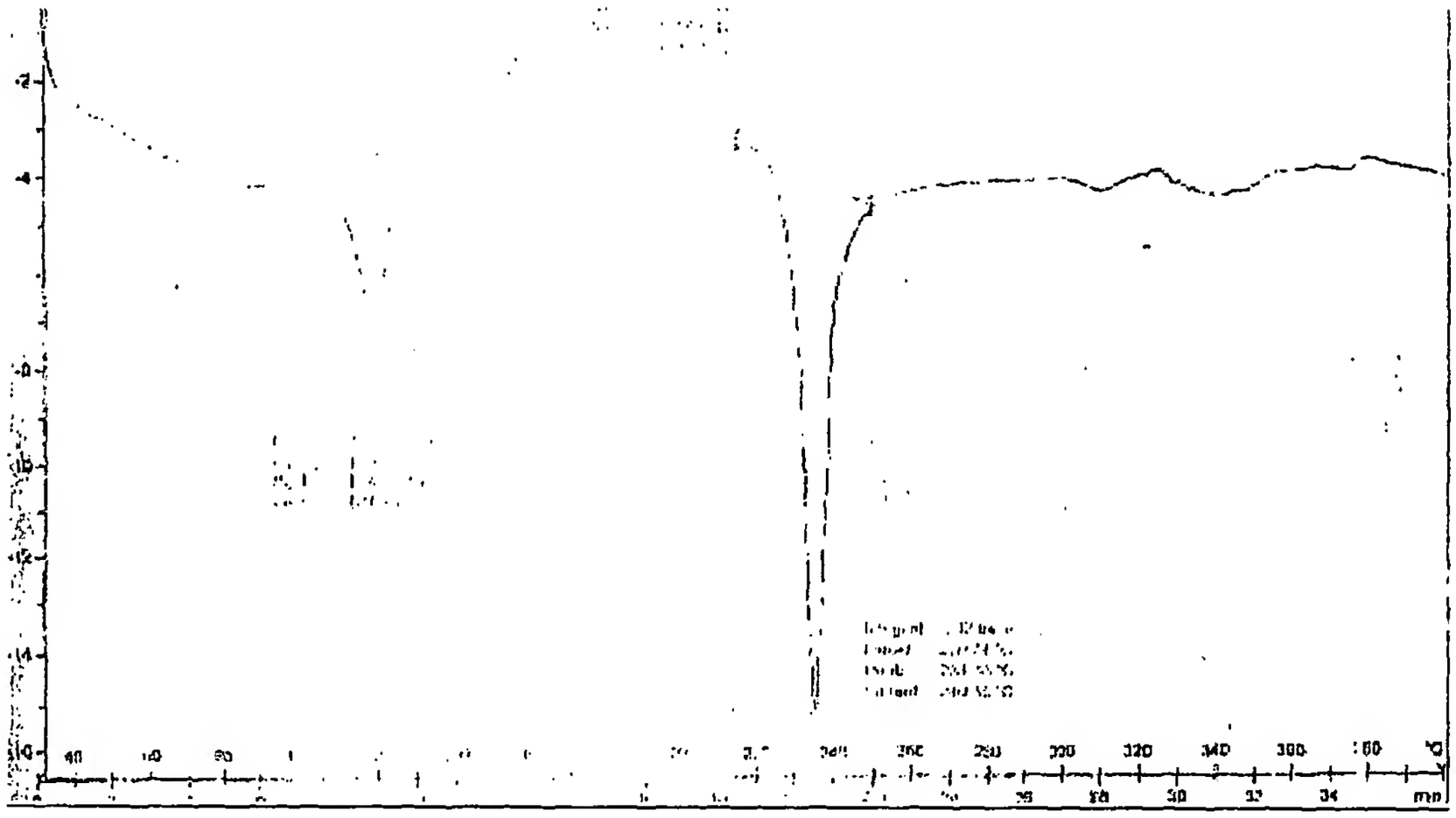


FIGURE 9

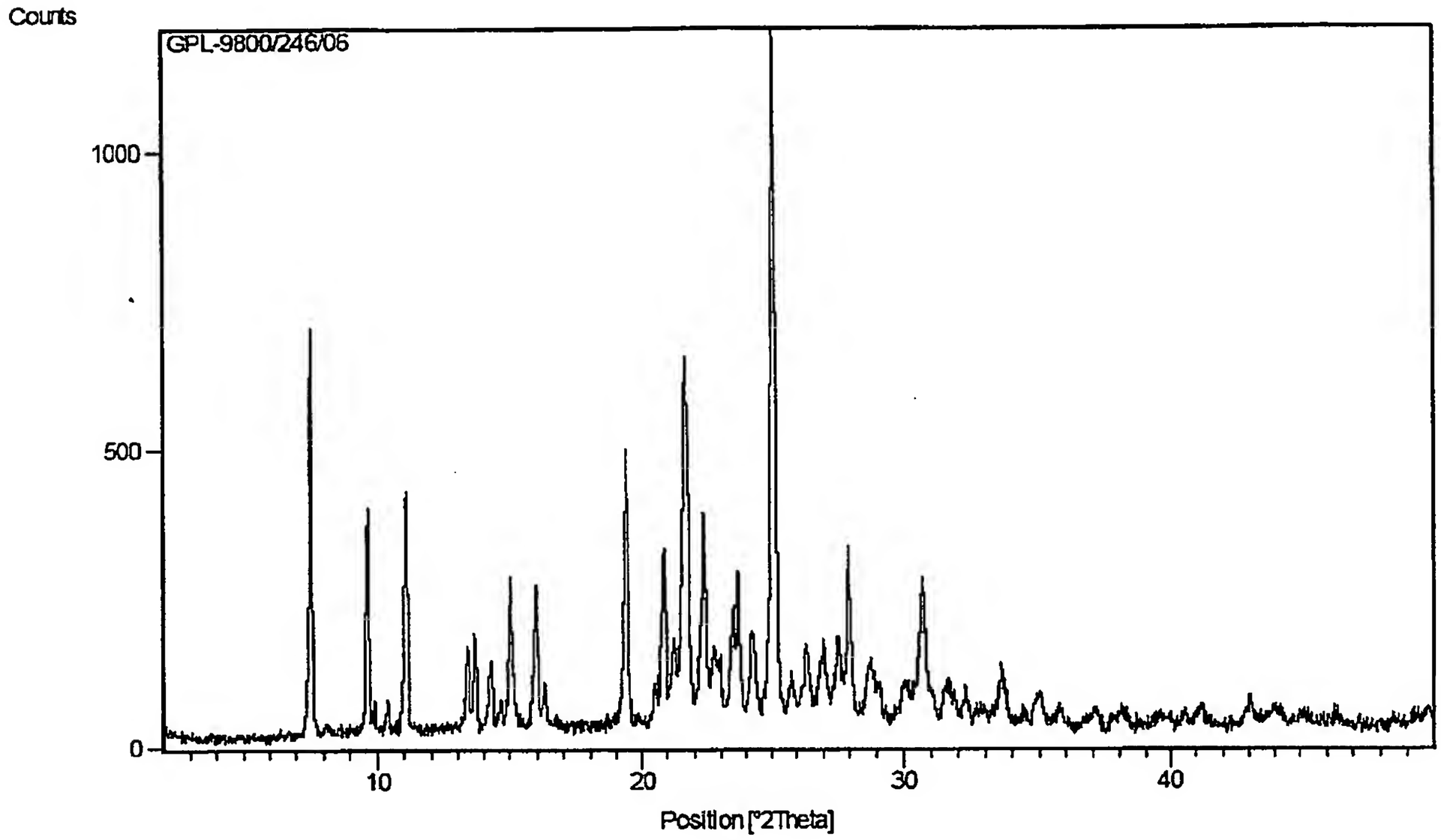


FIGURE 10